EXHIBIT "A"

DEPOSITION SUBJECT MATTER

Pursuant to Rule 30(b)(6), the deponent(s) must have knowledge of and shall be able to testify concerning the following subject matters related to TVT Products and Prolene Mesh defined in Paragraphs 4 through 10 of Notice of Deposition:

I. Mesh material used in Prolene Hernia Mesh Products and all of the TVT Products.

II. Mesh material used in any internal or Ethicon-funded study related to Prolene Hernia mesh and TVT Products.

III. Properties of the Prolene Hernia mesh and the TVT products including but not limited to the following characteristics:

a. Pore size
b. Weight
c. Elasticity
d. Flexural Rigidity
e. Biomechanical Properties
f. Construction of knitting

IV. Person Most Knowledgeable regarding "A 28-day intramuscular tissue reaction study in rats of polypropylene mesh from the TVT (Ulmsten) device (PSE 97-0197)" (See attached Exhibit A-1)

V. Person Most Knowledgeable regarding "The Science of "What's Left Behind"… Evidence & Follow-Up of Mesh Use for SUI" PowerPoint presentation by Nick Franco, MD. (See attached Exhibit A-2)

VI. Person Most Knowledgeable regarding "Gynecare TVT Tension-Free Support for Incontinence Professional Education Slides" Powerpoint presentation. (See attached Exhibit A-3)

VII. Person Most Knowledgeable regarding the mesh used in "A Multicenter Study of Tension-Free Vaginal Tape (TVT) for Surgical Treatment of Stress Urinary Incontinence" by U. Ulmsten. (See attached Exhibit A-4)

VIII. Person Most Knowledgeable regarding the mesh used in "Scandinavian Multicenter Study of the Tension Free Vaginal Tape Procedure" by M. Eriksson. (See attached Exhibit A-5)

IX. The complete design history file for Project Scion, TVT-PA and TVT+M, including each component part of the file, the custodian responsible for the file and the maintenance of the file.

EXHIBT A-1

ETHICON, INC.
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SOMERVILLE, NEW JERSEY 08876-0151

ETHICON INC.

JUN 1 8 1999

GLP ARCHIVES

June 16, 1999

GLP Archives PSE Acc No. 97-0197

Transfer of Original Paper Data to GLP Archives

PSE Accession No. 97-0197

A 28-DAY INTRAMUSCULAR TISSUE REACTION STUDY IN RATS OF POLYPROPYLENE MESH FROM THE TVT (ULMSTEN) DEVICE (PSE ACCESSION NO. 97-0197)

As of 6/16/1999 all original paper data for the above captioned accession number was transferred to the GLP Archives. The pagination of the Study Data Package is reflected in the attached table of contents. The completed files in the GLP Archives include 49 pages.

In accordance with GPS GLP SOP #2, the data now becomes the responsibility of the GLP Administrator and alternates.

Principal Investigator:

[signature] 6/16/99

Thomas A. Barbolt, Ph.D., D.A.B.T. Date

[signature] 6/18/99

Ellen M. Jones Date

GLP Archivist

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P.O. BOX 151
SOMERVILLE, NEW JERSEY 08876-0151

September 25, 1997

C. Linsky

PROTOCOL, PSE ACCESSION NO. 97-0197, PROJECT NO. 16672

A 28-DAY INTRAMUSCULAR TISSUE REACTION STUDY
IN RATS OF POLYPROPYLENE MESH FROM THE TVT (ULMSTEN) DEVICE

Attached is the protocol for the tissue reaction study indicated above.

Thomas A. Barbolt, Ph.D., D.A.B.T. — Date: 9/29/97
Study Director

cc: D. Burkley
J. Little
C. Norz
M. Rippy
N. Trenton
P. Trezza
CPC Central File
PSE Central File
GLP Archive (original)

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SOMERVILLE, NEW JERSEY 08876-0151

PROTOCOL, PSE ACCESSION NO. 97-0197, PROJECT NO. 16672

A 28-DAY INTRAMUSCULAR TISSUE REACTION STUDY IN RATS OF POLYPROPYLENE MESH FROM THE TVT (ULMSTEN) DEVICE

Sponsor

ETHICON, Inc.
PO Box 151
Somerville, NJ 08876-0151

Testing Facility

ETHICON, Inc
PO Box 151
Somerville, NJ 08876-0151

Proposed Date of *In Vivo* Phase Initiation: October 1, 1997

Proposed Date of *In Vivo* Phase Completion: October 30, 1997

THIS STUDY WILL BE CONDUCTED IN ACCORDANCE WITH THE GOOD LABORATORY PRACTICE REGULATIONS, 21 CFR PART 58.

Study Coordinator: [signature] 9/26/97
Katherine J. Hiemer, B.S.
Associate Scientist
Corporate Product Characterization
Date

Study Director: [signature] 9/29/97
Thomas A. Barbolt, Ph.D., D.A.B.T.
Principal Scientist
Corporate Product Characterization
Date

Study Pathologist: [signature] 9/29/97
Thomas A. Barbolt, Ph.D., D.A.B.T.
Principal Scientist
Corporate Product Characterization
Date

Approved: [signature] for Marian Rippy 9/29/97
Marian K. Rippy, D.V.M., D.A.C.V.P.
Director
Corporate Product Characterization
Date

PURPOSE

The purpose of this study is to assess the tissue reaction of polypropylene mesh from the TVT (Ulmsten) Device when implanted in rat gluteal muscle for up to 28 days, and to compare this reaction to that elicited by current production PROLENE* polypropylene mesh.

MATERIALS

Polypropylene mesh (test article) from the TVT Device, and PROLENE mesh (control article), after ethylene oxide sterilization will be supplied for implantation and are identified as follows:

Sample No.	ID	Description
1	EB1	Test Article Polypropylene mesh from the TVT Device
2	Lot #JJ2009	Control Article PROLENE mesh, Product Code PM-M 6" x 6" Sheet, Exp July 2001

CHARACTERIZATION/STABILITY

Analytical characterization and a statement of stability for the test and control articles will be provided in the final report of this study.

EXPERIMENTAL ANIMALS

Species: Female Long-Evans rats (HdsBlu:LE)
Weight: 250.0 - 350.0 grams
Age: Approx. 15 weeks
Supplier: Harlan Sprague Dawley, Inc.
Indianapolis, Indiana

Justification: Rats were chosen as the animal model for this study since reference data on tissue reaction to implants of biomaterials is readily available in this laboratory for this species.

EXPERIMENTAL DESIGN

Number of animals: 30 rats total (10 rats per period)
IACUC Approval Number PAF 97-11
Pain Category: II
Duration of study: 28 days with interim necropsy periods at 7, and 14 days postimplantation.

Animal identification: Each rat will have an identification number tattooed on its tail at implantation. This number will consist of a letter representing the year (K=1997), the accession number designation, and a sequence number for each animal. The rats will be numbered (K-197-01 to K-197-30) according to a computer-generated table that will randomly assign numbers to the order of implantation (Table 1). The animal number will determine the day of implantation and the postimplantation period to which the rat will be assigned (Attachment 1). Rats may be retattooed during the study if there is fading of the tattoo.

* Trademark

METHODS

This study will be conducted following the general procedures described in PSE GLP SOP No. 9" Implantation for Tissue Reaction/Absorption (TR/ABS) Studies" with the exception of the implantation procedure.

1. Sample Preparation:

All material will be supplied in appropriate sterile packaging.

Sample 1 - Polypropylene mesh from the Ulmsten Device: The mesh and the polyethylene (PE) sheath will be cut approximately 1 cm from the attachment to the needle. The mesh strip will be removed from the PE sheath and cut into pieces approximately 0.75 x 0.75 cm.

Sample 2 - PROLENE mesh: The mesh sheet will be cut into pieces approximately 0.75 x 0.75 cm.

2. Animal Selection:

A single batch of rats will be acclimated for a minimum of one week and a group of animals within the designated weight range will be selected from this batch of rats. Individual rats will be anesthetized with a mixture of KETASET[1] and ROMPUN[2].

3. Implantation:

A midline incision will be made in the skin over the sacral vertebral column. Skin will then be separated from the underlying connective tissue bilaterally to expose the gluteal muscles. Retractors will be placed to expose the muscles.

The superficial and medial gluteal muscles will be incised with a scalpel. A pocket will be created within the layers of the medial gluteal muscle using blunt/blunt delicate scissors. A piece of material will be placed in the pocket. Sample no. 1 will be implanted into the left muscle and sample no. 2 will be implanted into the right muscle. There will be one sample group; left sample no. 1 and right sample no. 2 (L1R2). Muscle incisions will be closed using size 5-0 ETHILON* nylon suture. Skin wounds will be closed with metal clips or staples.

The gluteal muscle was selected for implantation since this muscle has been used extensively for implantation of biomaterials in this laboratory and this tissue provides intimate exposure of suture to various mesenchymal tissues to mimic human exposure.

4. Animal Housing and Care:

Rats will be housed one per cage in suspended wire mesh cages for two weeks postoperatively and then housed five per cage in suspended wire mesh cages to provide environmental enrichment. Cage tags will show PSE accession number, sample number, technique, animal numbers, animal species/strain, date of implantation, postimplantation period and date of necropsy. Diet will consist of Certified Rodent Diet 5002[3] fed *ad libitum*. Municipal water will be supplied *ad libitum*. There are no known contaminants in the feed or water that could reasonably be expected to interfere with the conduct of this study.

*Trademark

[1]ketamine hydrochloride, Manufactured for Aveco Co., Inc., 800 5th St. N.W., Fort Dodge, Iowa, 50501 by Fort Dodge Laboratories, Inc., Fort Dodge, Iowa, 50501

[2]xylazine, Mobay Corp., Animal Health Division, Shawnee, Kansas, 66201

[3]PMI Feeds, Inc., 1401 S. Hanley RD., St. Louis, MO

The animals utilized in this study will be handled and maintained in accordance with current requirements of the Animal Welfare Act. Compliance with the above Public Laws will be accomplished by adhering to the Animal Welfare regulations (9 CFR) and conforming to the current standards promulgated in the Guide for the Care and Use of Laboratory Animals.

5. Clinical Observations:

After implantation, rats will be observed daily by animal care personnel to determine their general health status on the basis of food consumption, excretion, and general behavior according to PSE GLP SOP No. 5. Rats becoming ill during the study will be brought to the attention of the Study Director and examined by the Attending Veterinarian in charge of animal health. Treatment may be instituted if it is determined, in consultation with the Study Director, that the recommended treatment will not interfere with the conduct of the study.

6. Analgesics:

During the postsurgical survival period, butorphanol tartrate (0.04 mg/kg, SC), or acetaminophen (110-305 mg/kg, PO) may be administered based upon an evaluation of pain by the Study Director and/or the Attending Veterinarian.

7. Necropsy:

Rats sacrificed because of a moribund condition or dying during the study may be examined in order to determine the cause of death. Selected tissues may be saved at the discretion of the study director.

Rats will be sacrificed at their designated periods by inhalation of carbon dioxide (Attachment 1). Macroscopic observations of all implant sites will be recorded and implant sites will be excised as outlined in PSE SOP No. 10 with the exception of the Necropsy and Trim Record (Attachment 2). Gluteal muscles will be preserved in 10% buffered formalin fixative.

8. Histomorphology:

After fixation, a single transverse section perpendicular to the long axis of the implant sites will be trimmed from each gluteal muscle, embedded in paraffin, sectioned at 4-6 micrometers, and stained with hematoxylin and eosin according to procedures set forth in PSE SOP No. 10. Tissue reactions to the test and control articles will be evaluated histomorphologically.

RECORDS AND DATA HANDLING

The Study Director will initial and date any raw data or critical phase documentation on an available area of the form to indicate review and approval.

With the exception of ETHICON Laboratory Notebooks, all communications, reports, data, histologic slides, paraffin blocks and wet tissues as specified in PSE SOP No. 8, section 4.12, will be incorporated into the PSE GLP Archives according to the procedures detailed in PSE GLP SOP No. 2.

STATISTICAL EVALUATION OF RESULTS

Due to the subjective nature of histopathologic evaluation, it is not anticipated that statistical analysis will be necessary to evaluate the results.

ORDER OF IMPLANTATION

Implantation Day 1 Sequence Number	Animal Number	Implantation Day 2 Sequence Number	Animal Number
1	K-197-23	1	K-197-18
2	K-197-11	2	K-197-16
3	K-197-13	3	K-197-17
4	K-197-14	4	K-197-08
5	K-197-25	5	K-197-29
6	K-197-02	6	K-197-26
7	K-197-12	7	K-197-19
8	K-197-01	8	K-197-27
9	K-197-03	9	K-197-06
10	K-197-24	10	K-197-28
11	K-197-15	11	K-197-30
12	K-197-22	12	K-197-20
13	K-197-04	13	K-197-07
14	K-197-21	14	K-197-10
15	K-197-05	15	K-197-09

SCHEDULE OF EXPLANTS

SAMPLE NO.	PLACEMENT	MATERIAL DESCRIPTION	SAMPLE IDENTIFICATION
1	Left Gluteal Muscle	Polypropylene mesh from the TVT Device	EB1
2	Right Gluteal Muscle	PROLENE mesh Prod. Code PM-M, 6" x 6" Sheet, Exp July 2001	Lot #JJ2009

ANIMAL NUMBERS	SAMPLE GROUP	IMPLANT DATE	PI PERIOD	EXPLANT DATE
K-197-01 TO K-197-05	L1R2	10/1/97	7	10/8/97
K-197-06 TO K-197-10	L1R2	10/2/97	7	10/9/97
K-197-11 TO K-197-15	L1R2	10/1/97	14	10/15/97
K-197-16 TO K-197-20	L1R2	10/2/97	14	10/16/97
K-197-21 TO K-197-25	L1R2	10/1/97	28	10/29/97
K-197-26 TO K-197-30	L1R2	10/2/97	28	10/30/97

Attachment 2

NECROPSY AND TRIM RECORD

PSE ACC#: | Nx DATE: | DAYS PI:

TEST MATERIAL: | SPECIES: | SEX: Female

SPECIMEN: Gluteal Muscle | SACRIFICED: CO2

Animal #	Location	Sample #	Macroscopic Observations	D
	Left	1		
	Right	2		
	Left	1		
	Right	2		
	Left	1		
	Right	2		
	Left	1		
	Right	2		
	Left	1		
	Right	2		

KEY: D = Disposition N = No Abnormality Detected ✓ = Collected

Prosector(s) ____________ Date ____________

HISTOLOGY COMMENTS

Trimming: All tissues present Not Present	Embedding: No. Blocks	Quality Control: All tissues present Not Present
Other (specify):	Other (specify):	Other (specify):
Trimmed By:	Embedded By:	Sign Off:
Date:	Date:	Date:

ETHICON, INC.
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SOMERVILLE, NEW JERSEY 08876-0151

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December 23, 1997

To: GLP Archive for PSE ACCESSION NO. 97-0197

PROTOCOL DEVIATION, PSE ACCESSION NO. 97-0197, PROJECT NO. 16672

A 28-DAY INTRAMUSCULAR TISSUE REACTION STUDY
IN RATS OF POLYPROPYLENE MESH FROM THE TVT (ULMSTEN) DEVICE

Deviation:
The diagnosis and treatment record for animal no. K-197-08 dated 10/6/97 is missing a diagnosis and signature by the Attending Veterinarian.

Response:
The animal had a simple wound dehiscence which could not be repaired. The only recourse was to euthanize the animal. The Attending Veterinarian was not available to comment.

This protocol deviation is not considered to have an adverse impact on the conduct or outcome of the study.

12/23/97

Thomas A. Barbolt, Ph.D., D.A.B.T. Date
Study Director

cc: K. Hiemer
J. Little
PSE CF

ETHICON, INC.
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P.O. BOX 151
SOMERVILLE, NEW JERSEY 08876-0151

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January 30, 1998

C. Linsky

FINAL REPORT, PSE ACCESSION NO. 97-0197, PROJECT NO. 16672

A 28-DAY INTRAMUSCULAR TISSUE REACTION STUDY
IN RATS OF POLYPROPYLENE MESH FROM THE TVT (ULMSTEN) DEVICE

Attached is the final report for the tissue reaction study indicated above.

Thomas A. Barbolt, Ph.D., D.A.B.T. — 1/30/98
Study Director — Date

cc: D. Burkley (Appendices 1&2)
J. Little
C. Norz
N. Trenton
P. Trezza
PSE Central File
GLP Archive (original)
RDCF

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FINAL REPORT, PSE ACCESSION NO. 97-0197, PROJECT NO. 16672

A 28-DAY INTRAMUSCULAR TISSUE REACTION STUDY IN RATS OF POLYPROPYLENE MESH FROM THE TVT (ULMSTEN) DEVICE

Sponsor	Testing Facility
ETHICON, Inc. PO Box 151 Somerville, NJ 08876-0151	ETHICON, Inc PO Box 151 Somerville, NJ 08876-0151

Date of *In Vivo* Phase Initiation: October 1, 1997

Date of *In Vivo* Phase Completion: October 30, 1997

THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH THE GOOD LABORATORY PRACTICE REGULATIONS, 21 CFR PART 58.

Study Coordinator: [signature] 11/30/98
Katherine J. Hiemer, B.S.
Associate Scientist
Corporate Product Characterization
Date

Study Director: [signature] 11/30/98
Thomas A. Barbolt, Ph.D., D.A.B.T.
Research Fellow
Corporate Product Characterization
Date

Study Pathologist: [signature] 11/30/98
Thomas A. Barbolt, Ph.D., D.A.B.T.
Research Fellow
Corporate Product Characterization
Date

Approved: [signature] 11/30/98
Marian K. Rippy, D.V.M., Ph.D., D.A.C.V.P.
Director
Corporate Product Characterization
Date

PROFESSIONAL/SUPERVISORY PERSONNEL

Thomas A. Barbolt	- Research Fellow Preclinical Safety Evaluation
Katherine J. Hiemer	- Associate Scientist Preclinical Safety and Efficacy Evaluation
James McDivitt	- Research Fellow Analytical Chemistry
Marian K. Rippy	- Director Corporate Product Characterization
Lesley Traver	- Manager Analytical Chemistry/Product Performance Evaluation
Carol A. Norz	- Laboratory Animal Resources Coordinator Laboratory Animal Resources
Patricia E. Trezza	- Histotechnologist Corporate Product Characterization

SUMMARY

The tissue reaction to TVT mesh was characterized by generally mild chronic inflammation during the 28-day study which was comparable to the tissue reaction observed for PROLENE* polypropylene mesh, the comparative control. Myofiber regeneration and necrosis observed at 7 days postimplantation was attributed to tissue trauma related to the implantation procedure, and was not considered to be related to the presence of either implanted material. The resolution of the healing response of the muscle by 14 days postimplantation provided evidence that the presence of TVT mesh did not delay tissue healing when compared to PROLENE mesh.

*Trademark

PURPOSE

The purpose of this study was to assess the tissue reaction of polypropylene mesh from the TVT (Ulmsten) Device when implanted in rat gluteal muscle for up to 28 days, and to compare this reaction to that elicited by current production PROLENE mesh.

MATERIALS

Polypropylene mesh (test article) from the TVT Device, and PROLENE mesh (control article), after ethylene oxide sterilization was supplied for implantation and was identified as follows:

Sample No.	ID	Description
1	EB1	Test Article Polypropylene mesh from the TVT Device
2	Lot #JJ2009	Control Article PROLENE mesh, Product Code PM-M 6" x 6" Sheet, Exp July 2001

CHARACTERIZATION/STABILITY (Appendices 1 and 2)

Analytical characterization by infrared spectroscopy before implantation identified the test and control articles as polypropylene. The test and control articles were tested for residual ethylene oxide (EO), ethylene glycol (EG) and ethylene chlorohydrin (ECH) using gas chromatography. Residual EO, EG and ECH levels were each less than 1 ppm for the test and control articles. The demonstration of stability during the course of this study was determined to be unnecessary because polypropylene is a well known synthetic nonabsorbable polymeric material.

EXPERIMENTAL ANIMALS

Species: Female Long-Evans rats (HdsBlu:LE)
Weight: 288 - 316 grams
Age: Approx. 15 weeks
Supplier: Harlan Sprague Dawley, Inc.
Indianapolis, Indiana

Justification: This animal model was chosen for this study because historical data on tissue reaction in rats to implants of biomaterials is readily available in this laboratory.

EXPERIMENTAL DESIGN

Number of animals: 30 rats total (10 rats per period)
IACUC Approval Number PAF 97-11
Pain Category: II
Duration of study: 28 days with interim necropsy periods at 7 and 14 days postimplantation.

Animal identification: Each rat had an identification number tattooed on its tail at implantation. The rats were numbered (K-197-01 to K-197-30) according to a computer-generated table which randomly assigned numbers to the order of implantation. The animal number determined the postimplantation period to which the rat was assigned.

METHODS

This study was conducted following the general procedures described in PSE GLP SOP No. 9" Implantation for Tissue Reaction/Absorption (TR/ABS) Studies" with the exception of the implantation procedure which is described below.

1. Sample Preparation:
All material was supplied in appropriate sterile packaging.

Sample 1 - Polypropylene mesh from the Ulmsten Device: The mesh and the polyethylene (PE) sheath was cut approximately 1 cm from the attachment to the needle. The mesh strip was removed from the PE sheath and cut into pieces approximately 0.75 x 0.75 cm.

Sample 2 - PROLENE mesh: The mesh sheet was cut into pieces approximately 0.75 x 0.75 cm.

2. Animal Selection:
A single batch of rats was acclimated for a minimum of one week and placed in a large container. A group of animals within the designated weight range was selected from this batch of rats. Individual rats were removed without any apparent systematic bias and anesthetized with a mixture of KETASET[1] and ROMPUN[2].

3. Implantation:
A midline incision was made in the skin over the sacral vertebral column. Skin was then separated from the underlying connective tissue bilaterally to expose the gluteal muscles. Retractors were placed to expose the muscles. The superficial and medial gluteal muscles were incised with a scalpel. A pocket was created within the layers of the medial gluteal muscle using blunt/blunt delicate scissors. A piece of mesh material was placed in the pocket. Sample no. 1 was implanted in the left muscle and sample no. 2 was implanted in the right muscle. There was one sample group; left sample no. 1 and right sample no. 2 (L1R2). Muscle incisions were closed using size 5-0 ETHILON* nylon suture. Skin wounds were closed with metal clips.

The gluteal muscle was selected for implantation since this muscle has been used extensively for implantation of biomaterials in this laboratory and this tissue provides intimate exposure of suture to various mesenchymal tissues to mimic human exposure.

4. Animal Housing and Care:
Rats were housed one per cage in suspended wire mesh cages for two weeks postoperatively and then housed five per cage in suspended wire mesh cages to provide environmental enrichment. Cage tags identified all study information pertinent to the specific animal. Diet consisted of Certified Rodent Diet 5002[3] fed *ad libitum*. Municipal water was supplied *ad libitum*. There were no known contaminants in the feed or water that could reasonably be expected to interfere with the conduct of this study.

The animals utilized in this study were handled and maintained in accordance with current requirements of the Animal Welfare Act and its amendments. Compliance with the above Public Laws was accomplished by adhering to the Animal Welfare regulations (9 CFR) and conforming to the current standards promulgated in the Guide for the Care and Use of Laboratory Animals.

*Trademark

[1]ketamine hydrochloride, Manufactured for Aveco Co., Inc., 800 5th St. N.W., Fort Dodge, Iowa, 50501 by Fort Dodge Laboratories, Inc., Fort Dodge, Iowa, 50501

[2]xylazine, Mobay Corp., Animal Health Division, Shawnee, Kansas, 66201

[3]PMI Feeds, Inc., 1401 S. Hanley RD., St. Louis, MO

5. Clinical Observations:
After implantation, rats were observed daily by animal care personnel to determine their general health status on the basis of food consumption, excretion, and general behavior according to animal husbandry SOP's. Any clinical observations were brought to the attention of the Study Director.

6. Necropsy:
Rats were euthanized at their designated periods by inhalation of carbon dioxide. Macroscopic observations of all implant sites were recorded and implant sites were excised as generally outlined in PSE SOP No. 10. Gluteal muscles were preserved in 10% buffered formalin fixative.

7. Histomorphology:
After fixation, a single transverse section perpendicular to the long axis of the implant sites was trimmed from each gluteal muscle, embedded in paraffin, sectioned at 4-6 micrometers, and stained with hematoxylin and eosin according to procedures set forth in PSE SOP No. 10. Tissue reactions to the test and control articles were evaluated histomorphologically.

Histomorphologic observations were scored according to the following grading system based on the intensity and extent of the observation: Minimal = 1; Mild (Slight) = 2; Moderate = 3; and Marked = 4.

RESULTS

1. Clinical Observations:
Due to an open incision that could not be repaired, one animal (K-197-08) was euthanized at 4 days postimplantation. No other clinical observations were recorded for any animal. All rats were in good general condition at scheduled necropsies.

2. Macroscopic Observations:
No macroscopic abnormalities were detected at the implantation sites for the test or control articles at any explant period.

3. Histomorphologic Observations:
Histomorphologic observations are summarized for comparisons in Table 1 and are presented for individual animals in Attachment 1.

At 7 days postimplantation, the tissue reaction to the test article was characterized by minimal to mild chronic inflammation (9/9), minimal to moderate myofiber regeneration (9/9), and minimal to mild myofiber necrosis (2/9). The chronic inflammation consisted of variable amounts of chronic inflammatory cells and fibrosis surrounding and adjacent to the implant. At 14 days postimplantation, the tissue reaction was characterized by minimal to mild chronic inflammation (10/10). At 28 days postimplantation, the tissue reaction was characterized by mild chronic inflammation (10/10).

At 7 days postimplantation, the tissue reaction to the control article was characterized by mild chronic inflammation (9/9), minimal to moderate myofiber regeneration (9/9), and minimal myofiber necrosis (1/9). At 14 days postimplantation, the tissue reaction was characterized by minimal to mild chronic inflammation (10/10). At 28 days postimplantation, the tissue reaction was characterized by mild chronic inflammation (10/10).

CONCLUSION

The tissue reaction to TVT mesh was characterized by generally mild chronic inflammation during the 28-day study which was comparable to the tissue reaction observed for PROLENE mesh, the comparative control. Myofiber regeneration and necrosis observed at 7 days postimplantation was attributed to tissue trauma related to the implantation procedure, and was not considered to be related to the presence of either implanted material. The resolution of the healing response of the muscle by 14 days postimplantation provided evidence that the presence of TVT mesh did not delay tissue healing when compared to PROLENE mesh.

COMMENT

A pre-study meeting was held on September 26, 1997 to communicate pertinent areas of the protocol to those associates anticipated to participate.

Occasional minor deviations from the protocol occurred and are documented in the raw data. These deviations were considered not to have had an impact on the outcome of the study or upon the interpretation of the results.

RECORDS AND DATA HANDLING

The Study Director initialed and dated any raw data or critical phase documentation on an available area of the form to indicate review and approval.

With the exception of ETHICON Laboratory Notebooks, all communications, reports, data, histologic slides, paraffin blocks and wet tissues as specified in PSE SOP No. 8, section 4.12, will be incorporated into the PSE GLP Archives according to the procedures detailed in PSE GLP SOP No. 2.

STATISTICAL EVALUATION OF RESULTS

Due to the qualitative nature of histomorphologic evaluation, statistical analysis of the data was not needed to evaluate the results.

Summary of Histomorphologic Observations for Intramuscular Implantation Sites with TVT Polypropylene Mesh

MATERIAL	OBSERVATIONS *	DAYS POSTIMPLANTATION 7	14	28
TEST ARTICLE		(9)	(10)	(10)
	Chronic inflammation	9/1.89	10/1.80	10/2.00
	Minimal	1	2	0
	Mild	8	8	10
	Myofiber regeneration	9/2.11	0/0	0/0
	Minimal	2	0	0
	Mild	4	0	0
	Moderate	3	0	0
	Myofiber necrosis	2/0.33	0/0	0/0
	Minimal	1	0	0
	Mild	1	0	0
CONTROL ARTICLE		(9)	(10)	(10)
	Chronic inflammation	9/2.00	10/1.70	10/2.00
	Minimal	0	3	0
	Mild	9	7	10
	Myofiber regeneration	9/1.89	0/0	0/0
	Minimal	3	0	0
	Mild	4	0	0
	Moderate	2	0	0
	Myofiber necrosis	1/0.11	0/0	0/0
	Minimal	1	0	0

* Total incidence/Mean severity score for number of sites examined
( ) = Number of sites examined

Individual Animal Histomorphologic Observations for Intramuscular
Implantation Sites with TVT Polypropylene Mesh

ANIMAL NO.	MATERIAL	DAYS PI	OBSERVATIONS
K-197-01	TEST ARTICLE	7	Mild Chronic inflammation Mild Myofiber regeneration Minimal Myofiber necrosis
	CONTROL ARTICLE		Mild Chronic inflammation Mild Myofiber regeneration Minimal Myofiber necrosis
K-197-02	TEST ARTICLE		Mild Chronic inflammation Mild Myofiber regeneration
	CONTROL ARTICLE		Mild Chronic inflammation Mild Myofiber regeneration
K-197-03	TEST ARTICLE		Mild Chronic inflammation Mild Myofiber regeneration
	CONTROL ARTICLE		Mild Chronic inflammation Moderate Myofiber regeneration
K-197-04	TEST ARTICLE		Mild Chronic inflammation Mild Myofiber regeneration Mild Myofiber necrosis
	CONTROL ARTICLE		Mild Chronic inflammation Moderate Myofiber regeneration
K-197-05	TEST ARTICLE		Mild Chronic inflammation Moderate Myofiber regeneration
	CONTROL ARTICLE		Mild Chronic inflammation Minimal Myofiber regeneration
K-197-06	TEST ARTICLE		Mild Chronic inflammation Moderate Myofiber regeneration
	CONTROL ARTICLE		Mild Chronic inflammation Mild Myofiber regeneration
K-197-07	TEST ARTICLE		Minimal Chronic inflammation Minimal Myofiber regeneration

Study Pathologist [signature] 1/30/98
Date

Individual Animal Histomorphologic Observations for Intramuscular Implantation Sites with TVT Polypropylene Mesh

ANIMAL NO.	MATERIAL	DAYS PI	OBSERVATIONS
K-197-07	CONTROL ARTICLE	7	Mild Chronic inflammation Minimal Myofiber regeneration
K-197-08			Euthanized on Day 4 - No tissues collected
K-197-09	TEST ARTICLE		Mild Chronic inflammation Moderate Myofiber regeneration
	CONTROL ARTICLE		Mild Chronic inflammation Minimal Myofiber regeneration
K-197-10	TEST ARTICLE		Mild Chronic inflammation Minimal Myofiber regeneration
	CONTROL ARTICLE		Mild Chronic inflammation Mild Myofiber regeneration
K-197-11	TEST ARTICLE	14	Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-12	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-13	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-14	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-15	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Minimal Chronic inflammation
K-197-16	TEST ARTICLE		Minimal Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation

Study Pathologist [signature] 1/30/98
Date

Individual Animal Histomorphologic Observations for Intramuscular Implantation Sites with TVT Polypropylene Mesh

ANIMAL NO.	MATERIAL	DAYS PI	OBSERVATIONS
K-197-17	TEST ARTICLE	14	Minimal Chronic inflammation
	CONTROL ARTICLE		Minimal Chronic inflammation
K-197-18	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-19	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Minimal Chronic inflammation
K-197-20	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-21	TEST ARTICLE	28	Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-22	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-23	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-24	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-25	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-26	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-27	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation

Study Pathologist [signature] 1/30/98
Date

Individual Animal Histomorphologic Observations for Intramuscular Implantation Sites with TVT Polypropylene Mesh

ANIMAL NO.	MATERIAL	DAYS PI	OBSERVATIONS
K-197-28	TEST ARTICLE	28	Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-29	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation
K-197-30	TEST ARTICLE		Mild Chronic inflammation
	CONTROL ARTICLE		Mild Chronic inflammation

Study Pathologist [signature] 11/30/98
Date

ETHICON, INC.
a Johnson & Johnson company
P.O. BOX 151
SOMERVILLE • NEW JERSEY • 08876-0151

October 27, 1997

CC: CPC-CF

T. Barbolt

CHARACTERIZATION OF ULMSTEN POLYPROPYLENE MESH USED FOR BIOCOMPATIBILITY STUDIES

The following sample has been characterized 'prior to use' for the following safety study, PSE Accession No. 97-0197:

Product Name: ULMSTEN polypropylene mesh
Sterilization: Ethylene Oxide, Non-CFC
Product Number: EB1
Analytical Ref #: SR # 38902

The following sample of ULMSTEN polypropylene mesh (manufactured using the same raw material as PROLENE mesh) was received for characterization: A strip of mesh woven from unpigmented monofilament fibers fastened to two large (4"+) metal needles.

Identity of the ULMSTEN polypropylene mesh material was determined by infrared spectroscopy. The mesh material was identified as polypropylene.

The product was tested for residual ethylene oxide (EO), ethylene glycol (EG) and ethylene chlorohydrin (ECH) using gas chromatography. Residual EO, EG and ECH levels were each <1 ppm.

Polypropylene is a well known synthetic nonabsorbable polymeric material used in many medical applications, such as in sutures and syringes. ETHICON's PROLENE mesh and sutures have been marketed for many years with stability study data supporting 5-year expiry dating. Consequently, the demonstration of stability during the course of a safety study for the ambient dry storage of this polypropylene mesh was not necessary.

Daniel F. Burkley, MS
Senior Scientist
Corporate Product Characterization

ETHICON, INC.
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October 27, 1997

CC: CPC-CF

T. Barbolt

CHARACTERIZATION OF PROLENE* POLYPROPYLENE MESH USED FOR BIOCOMPATIBILITY STUDIES

The following sample has been characterized 'prior to use' for the following safety study, PSE Accession No. 97-0197:

Product Name: PROLENE polypropylene mesh, 6" x 6"
Sterilization: Ethylene Oxide, Non-CFC
Product Number: Product Code PM-M, Lot JJ2009
Analytical Ref #: SR # 38901

The following sample of PROLENE polypropylene mesh was received for characterization: A 6" x 6"square of mesh woven from unpigmented monofilament fibers.

Identity of the PROLENE polypropylene mesh material was determined by infrared spectroscopy. The mesh material was identified as polypropylene.

The product was tested for residual ethylene oxide (EO), ethylene glycol (EG) and ethylene chlorohydrin (ECH) using gas chromatography. Residual EO, EG and ECH levels were each <1 ppm.

Polypropylene is a well known synthetic nonabsorbable polymeric material used in many medical applications, such as in sutures and syringes. ETHICON's PROLENE mesh and sutures have been marketed for many years with stability study data supporting 5-year expiry dating. Consequently, the demonstration of stability during the course of a safety study for the ambient dry storage of this polypropylene mesh was not necessary.

Daniel F. Burkley, MS
Senior Scientist
Corporate Product Characterization

*Trademark

PSE 97-0197

QUALITY ASSURANCE STATEMENT

ACCESSION NO.: PSE 97-0197

STUDY TITLE: A 28-Day Intramuscular Tissue Reaction Study in Rats of Polypropylene Mesh from the TVT (Ulmsten) Device

****

The above mentioned study was inspected and the findings reported to Management and the Study Director on the dates listed below:

PHASE	DATE OF INSPECTION/REPORT
Protocol.	09/26/07
In-Life Procedures.	10/01/97
In-Life Procedures.	10/02/97
Necropsy.	10/29/97
Raw data, Final Report.	01/16/98
Characterization data, report.	01/26/98
Issued report to Management & Study Director.	01/26/98

[signature] 01.30.98

Janis A. Little — Date
Senior Project Manager
Regulatory Affairs

ETHICON, INC.
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P.O. BOX 151
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December 4, 1997

To: Study File for PSE 97-0197

Re: Environmental Conditions During Study PSE 97-0197

During the conduct of this study, the average daily relative humidity (Room 340) and the average daily temperatures were within the target limits recommended by the Guide for the Care and Use of Laboratory Animals.

C Norz 12-4-97
C. Norz, L.A.T.
Laboratory Animal Resources Coordinator

cc: T. Barbolt
K. Hiemer

DOCUMENTATION OF ERRORS IN RAW DATA GENERATED FOR GLP STUDIES

In accordance with GLP requirements, any data that is marked out and/or changed for any reason must be made in such a manner as not to obscure the original entry, must be initialed and dated and the reason for the change noted. To facilitate this requirement, Preclinical Safety & Efficacy should use a coding system to document the reasons for changing the data. The series listed below should include the majority of reasons. If none of these reasons are accurate, then the reason should be written out on the data as a footnote.

(1) Inadvertently entered incorrect original data.

(2) Inadvertently transposed the wrong data or transposition error.

(3) Inadvertently recorded data in wrong location or wrong book.

(4) Changed wording, sentence structure or description for greater clarity.

(5) Spelling error.

(6) Inadvertently not recorded at time of initial observation.

(7) Incorrect calculation.

(8) Footnote or attachment.

(9) Correction to pre-printed form.

A COPY OF THIS CODE SHOULD BE MAINTAINED WITH THE RAW DATA FOR EACH STUDY.

13

Author: Katherine Hiemer at 50RESEARCH2
Date: 9/22/97 2:28 PM
Priority: Normal
TO: Carol Norz at 50RESEARCH3
TO: Janis Little
TO: Paul Mazzucco
TO: Matthew Gilvey at 50RESEARCH1
TO: Nancy Trenton at 50RESEARCH3
TO: Patricia Trezza at 50RESEARCH3
CC: Thomas Barbolt at 50RESEARCH1 97-0197 CAO 9/22/97
Subject: Pre-Study Meeting for ~~97-0192~~ - Tissue Reaction Study

------------------------------------ Message Contents ------------------------------------

A GLP tissue reaction study for polypropylene mesh from the TVT (Ulmsten) Device has been scheduled for implantation October 1 and 2.

I have scheduled the pre-study meeting for Friday September 26 from 10:00-11:00am in the ERF Conference room. Please pass this cc:mail on to anyone in your area who may be participating in this study. The protocol should be issued by Friday.

Thanks
Kathy

9/26/97

Attendance at Pre-study meeting for 97-0197

1	Nancy Ironton
2	Katherine Adams
3	[illegible]
4	[illegible]
5	Luez J. Marin
6	Arnaud de Marco
7	D Bartlett
8	
9	
10	
11	
12	
13	
14	
15	

PERSONNEL ROSTER PSE 97-0197

The following personnel are (or may be) involved in the conduct of PSE Accession No. 97-0197. Each person involved in this study has reviewed the PSE SOP(s) and those areas of the protocol pertaining to his or her area of involvement. Their signatures and initials below acknowledge these reviews and are representative of those being used in the raw data.

Print Name	Signature	Initials
MATTHEW GILVEY	[signature]	MVG
Paul R Mazzucco	[signature]	PM
JOZS MARIN	[signature]	JM
Arnold De Marco	[signature]	ADM
T. A. Barbolt	[signature]	TAB
Katherine Hiemer	[signature]	KH
Nancy Trenton	[signature]	NT
Carol Norz	[signature]	CN
Richard Savage	[signature]	RS
Victor Yarnall	[signature]	VY
HWASON GODDARD	[signature]	HG
Diana S Merrill	[signature]	DM
NORMAN B. GUILLOUD	[signature]	NBG
PATRICIA E. TREZZA	[signature]	PET

Harlan SPRAGUE DAWLEY

Harlan Sprague Dawley, Inc.
Customer Services Center
Indianapolis, Indiana
Phone (317) 894-7025
Fax (317) 894-1840

Packing Slip

08/26/97

Harlan Order No.
161119 SO

Rec'd 206 ADM

Sold To: ETHICON INC
ATTN: CAROL NORZ
DEPT CPC RTE 22
SOMERVILLE NJ 088760000

Ship To: ETHICON INC
ROUTE 22
SOMERVILLE NJ 088760000

EXACT COPY OF ORIGINAL 10/24/97

Date Ordered	Customer Order No.	Ordered By	Ship Via	F.O.B.	Customer Code	Date Shipped
06/30/97	VERBAL	N/A 000 0000000	Company Truck	Shipping Pt.	1517	08/31/97

Quantity	Sex	Item Code	Description	Researcher	Department	Ship Loc	Area	Unit Price
200	Female	14010F	HsdBlu:LE 250-274 Grams FROM 217	CAROL		217		[redacted]
20	N/A	99991	Filtered Shipping Container	CAROL		217		
40	N/A	30000	Water Kits FROM 217 Freight Code 350	CAROL		217		

Avg WT
235
240
238
238
230
250
226
248
235
242
2382 ÷ 10 = 238.2

Batch # 9-2-97-A
Amount Received 206
Date 9/2/97
Initials ADM

Donald DeMarco

[redacted]

Code Thank You! 003/037

Total Number of Containers 20

ANIMAL RESOURCES MANAGEMENT

BATCH RECORD

BATCH NO. 9-2-97-A NO. MALES -0- PAGE 1 of 2

SUPPLIER Harlan Sprague Dawley SPECIES/STRAIN Rat LE NO. FEMALES 206 AVG. WT. 238.2

CHECK APPROPRIATE ENTRY

GENERAL CONDITION: ✓GOOD OTHER

SKIN/HAIR COAT: ✓NORMAL OTHER

NASAL/OCULAR EXUDATES: ✓NONE OTHER

RESPIRATION: ✓NORMAL OTHER

FECES/URINE: ✓NORMAL OTHER

ABNORMAL LOCOMOTION: ✓NONE OTHER

ABNORMAL BEHAVIOR: ✓NONE OTHER

OTHER COMMENTS:

ALL ANIMALS RECEIVED IN APPARENT GOOD CONDITION, EXCEPT AS NOTED

Arnold J DeMarco 9/2/97

NUMBER PLACED ON STUDY	ANES. DEATH	STOCK DEATH	ACCESSION NO.	STUDY DIRECTOR	DATE	ACTIVITY NO. OR IACUC APPROVAL DATE	COMMENTS
4			K0496	J. Walker JW	9/26/97	PAF97-2	
4			K0497	J. Walker JW	9/29/97	PAF97-2	
14	3		K0498	J. Walker JW	9/29/97	PAF97-2	
4			K0499	J. Walker JW	9/29/97	PAF97-2	
4			K0500	J. Walker JW	9/29/97	PAF97-2	
4			K0501	J. Walker JW	9/30/97	PAF97-2	
12			K0502	J. Walker JW	9/30/97	PAF97-2	
18			K0503	J. Walker JW	9/30/97	PAF97-2	EXACT COPY OF ORIGINAL KR 11.24.97
15			97-0197	T. Barbolt JW	10/1/97	PAF97-11	
15			97-0197	T. Barbolt JW	10/2/97	PAF97-11	
2			K0504	J. Walker JW	10/3/97	PAF97-2	
2			K0505	J. Walker JW	10/3/97	PAF97-2	
4			K0506	J. Walker JW	10/3/97	PAF97-2	
12			K0507	J. Walker JW	10/6/97	PAF97-2	
4			K0508	J. Walker JW	10/8/97	PAF97-2	
6			K0509	J. Walker JW	10/8/97	PAF97-2	
2			K0510	J. Walker JW	10/8/97	PAF97-2	
4			K0511	J. Walker JW	10/8/97	PAF97-2	
8			K0512	J. Walker JW	10/8/97	PAF97-2	
4			K0513	J. Walker JW	10/9/97	PAF97-2	

BATCH RECORD BATCH NO. 9-2-97A PAGE 2 OF 2

NUMBER PLACED ON STUDY	NUMBER ANES. DEATH	NUMBER STOCK DEATH	ACCESSION NO.	STUDY DIRECTOR	DATE	ACTIVITY NO. OR IACUC APPROVAL DATE	COMMENTS
16			K0514	J. Trauer JH	10/9/97	PAF97-2	
22			K0515	J. Trauer JH	10/9/97	PAF97-2	
4			K0516	J. Trauer JH	10/10/97	PAF97-2	
6			K0517	J. Trauer JH	10/10/97	PAF97-2	
6			K0518	J. Trauer JH	10/13/97	PAF97-2	
2			K0519	J. Trauer JH	10/13/97	PAF97-2	
5			K0520	J. Trauer JH	10/13/97	PAF97-2	
					/ /		
					/ /		
					/ /		
					/ /		
					/ /	EXACT COPY OF ORIGINAL	
					/ /		
					/ /		KA 11/24/97
					/ /		
					/ /		
					/ /		
					/ /		
					/ /		
					/ /		

Laboratory Animal Resources

Animal Body Weight Record

Study Director: T. Barbolt

Species: Rat

Sex: Female

Strain: L.E.

Batch #: 9-2-97A

Quantity: 15

Body Weight: (g)

306
300
314
316
308
316
314
308
315
309
301
310
314
305
299

Study Coordinator: Katherine Hiemer

Instrument Control #: 64506-00SWSE-03

Accession # : 97-0197

JJB 1/26/98

The animals listed above ranged in weight from 299 - 316 g averaging 309 grams.

This study was weighed by: JH Date: 10-1-97

Laboratory Animal Resources

Animal Body Weight Record

Study Director: T. Barbolt

Study Coordinator: Kathy ~~Heimer~~ Hiemer (5) 10-2-97

Species: Rat

Instrument Control #: 64506-00-SWSE-03

Sex: Female

Accession #: 97-0197

Strain: L.E.

Batch #: 9-~~02~~ 2-97A (correction initialed, 1/29/98)

Quantity: 15

Body Weight: (g)

299
300
300
299
311
293
299
298
295
294
296
288
296
293
300

(initialed, 1/26/98)

The animals listed above ranged in weight from 288 - 311 g averaging ~~297.4~~ 297 (1) (initialed 10-2-97) grams.

This study was weighed by: (initials) Date: 10-2-97

ANESTHESIA AND SURGERY RECORD

STUDY INFORMATION

PSE Accession #:	PSE 97-0197	Date of Implantation:	10/01/97
Test Material(s):	Polypropylene mesh from the Ulmsten device		
Sample Preparation:	cut mesh into pieces approximately 0.75 x 0.75 cm.		

ANIMAL INFORMATION

SOP #:	PSE GLP SOP No. 9: "Implantation for Tissue Reaction/Absorption (TR/ABS) Studies"		
Species:	Long Evans Rat - HSD	Batch Number:	9-2-97A
Sex:	Female	Animal Numbers:	K-197-01 → K-197-05 K-197-11 → K-197-15 KCM 10/1/97 K-197-21 TO K-197-25
Weight Range:	250.0-350.0 g	Average Weight:	309 g.

ANESTHESIA

Anesthetic Mixture:	60 mg/kg Ketamine (100 mg/ml) 10 mg/kg Xylazine (20 mg/ml)		
Route of Administration:	IP	Dosage Administered/Animal:	0.33 ml

SURGICAL NOTES

Operator A:	K. Hiemer	Operator B:	
Sample #'s:	1,2	Sample #'s:	
Anesthetist(s):	N. Trenton M. Gilvey		
Tattooist	Paul Mazzucco		

OTHER

Matt Gilvey closed the rats with 9mm stainless steel wound clips. [initials] 10/1/97

ETHILON size 5-0 Lot No. - GBR341V (Prod Code 698H)

Signature [signature] Date 10/2/97

ANESTHESIA AND SURGERY RECORD

STUDY INFORMATION

PSE Accession #: PSE 97-0197
Date of Implantation: 10/02/97
Test Material(s): Polypropylene mesh from the Ulmsten device
Sample Preparation: cut mesh into pieces approximately 0.75 x 0.75 cm.

ANIMAL INFORMATION

DJ 3/29/98 (1)

SOP #: PSE GLP SOP No. 9: "Implantation for Tissue Reaction/Absorption (TR/ABS) Studies"
Species: Long Evans Rat - HSD
Batch Number: 9-~~22~~ 2-97A
Sex: Female
Animal Numbers: K-197-06 TO K-197-10; K-197-16 TO K-197-20; K-197-26 TO K-197-30
Weight Range: 250.0-350.0 g
Average Weight: 297 g.

ANESTHESIA

Anesthetic Mixture: 60 mg/kg Ketamine (100 mg/ml)
10 mg/kg Xylazine (20 mg/ml)
Route of Administration: IP
Dosage Administered/Animal: 0.32 ml

SURGICAL NOTES

Operator A: K. Hiemer
Sample #'s: 1,2
Operator B:
Sample #'s:

Anesthetist(s): N. Trenton
McGilvey

Tattooist: Paul Mazzucco

OTHER

Matt Gilvey closed skin w/9mm stainless steel wound clips

DJ 10/2/97

ETHILON size 5-0 Lot GBR341 (Prod Code 698H)

Signature: Kathleen J Hiemer
Date: 10/2/97

Ethicon Laboratory Animal Resources
Rodent Clinical Observation Form

Acc # PSE 97-0197

Room No. 340

Species/Strain Rat / L.E.

Month October

Batch # 9 / ~~02~~ 2 / 97A WD3 1-29-98

Year 1997

Animal #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
K-197-06		PX1	X	X	X	X	X	X	XE																						
K-197-07		PX1	X	X	X	X	X	X	XE																						
K-197-08		PX1	X	X	X	E	(6) JH 10-09-97																								
K-197-09		PX1	X	X	X	X	X	X	XE																						
K-197-10		PX1	X	X	X	X	X	X	XE																						
K-197-16		PX1	X	X	X	X	X	X	X	X	X	X	X	X	XG	XE															
K-197-17		PX1	X	X	X	X	X	X	X	X	X	X	X	X	XG	XE															
K-197-18		PX1	X	X	X	X	X	X	X	X	X	X	X	X	XG	XE															
K-197-19		PX1	X	X	X	X	X	X	X	X	X	X	X	X	XG	XE															
K-197-20		PX1	X	X	X	X	X	X	X	X	X	X	X	X	XG	XE															
K-197-26		PX1	X	X	X	X	X	X	X	X	X	X	X	X	XG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	XE	
K-197-27		PX1	X	X	X	X	X	X	X	X	X	X	X	X	XG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	XE	
K-197-28		PX1	X	X	X	X	X	X	X	X	X	X	X	X	XG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	XE	
K-197-29		PX1	X	X	X	X	X	X	X	X	X	X	X	X	XG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	XE	
K-197-30		PX1	X	X	X	X	X	X	X	X	X	X	X	X	XG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	XE	
Initials		JH	JH	Pm	Pm	JH	[illegible]	JH	JH	JH	JH	JH	JH	JH	JH	JH	JH	Pm	Pm	JH	JH	JH	JH	JH	Pm	Pm	JH	JH	JH	JH	

Observation codes:
R = Received
X = No observed abnormality
~~D = Death documentation form initiated~~ WD3 1/26/98
P = Placed on study
T = Treatment
E = Euthanized
S = Study complete

Other: Code	Observation
I	Individually Housed
G *	5/cage

* Animals housed 5/cage on day 13 of study (JH 1-26-98)

Ethicon Laboratory Animal Resources
Rodent Clinical Observation Form

Acc # PSE 97-0197

Species/Strain Rat / L.E.

Batch # 9 / 02 / 97A [illegible] 1/29/98

Room No. 340

Month October

Year 1997

Animal # / Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
K-197-01	P X I	X	X	X	X	X	X	X E																							
K-197-02	P X I	X	X	X	X	X	X	X E																							
K-197-03	P X I	X	X	X	X	X	X	X E																							
K-197-04	P X I	X	X	X	X	X	X	X E																							
K-197-06	P X I	X	X	X	X	X	X	X E																							
K-197-11	P X I	X	X	X	X	X	X	X	X	X	X	X	X	X	X E																
K-197-12	P X I	X	X	X	X	X	X	X	X	X	X	X	X	X	X E																
K-197-13	P X I	X	X	X	X	X	X	X	X	X	X	X	X	X	X E																
K-197-14	P X I	X	X	X	X	X	X	X	X	X	X	X	X	X	X E																
K-197-15	P X I	X	X	X	X	X	X	X	X	X	X	X	X	X	X E																
K-197-21	P X I	X	X	X	X	X	X	X	X	X	X	X	X	X	X Fs	X	X	X	X	X	X	X	X	X	X	X	X	X	X E		
K-197-22	P X I	X	X	X	X	X	X	X	X	X	X	X	X	X	X Fs	X	X	X	X	X	X	X	X	X	X	X	X	X	X E		
K-197-23	P X I	X	X	X	X	X	X	X	X	X	X	X	X	X	X Fs	X	X	X	X	X	X	X	X	X	X	X	X	X	X E		
K-197-24	P X I	X	X	X	X	X	X	X	X	X	X	X	X	X	X Fs	X	X	X	X	X	X	X	X	X	X	X	X	X	X E		
K-197-25	P X I	X	X	X	X	X	X	X	X	X	X	X	X	X	X Fs	X	X	X	X	X	X	X	X	X	X	X	X	X	X E		
Initials	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		

Observation codes:

R = Received
X = No observed abnormality
~~D = Death documentation form initiated~~
P = Placed on study
T = Treatment
E = Euthanized
S = Study complete

[illegible] 1/28/98

Other:

Code	Observation
I	Individually Housed
Fs	5 / cage

DIAGNOSIS AND TREATMENT RECORD

BATCH # 9-2-97A

ACC # 97-0197 ANIMAL # ~~0804~~ F-197-08 SPECIES Rat ROOM 340

DESCRIPTION OF PROBLEM: Open Incision — DATE: 10.6.97

[signature] LAR Personnel

DIAGNOSIS: DATE:

TREATMENT PRESCRIBED: Euthanize - not able to reclip — DATE:

[signature] 10/6/97 Study Director

Attending Veterinarian

Date	T	P	R	Treatment / Clinical Observations	Initials
10-6-97				Euthanized animal	[initials]

Attachment 2

NECROPSY AND TRIM RECORD

PSE ACC#: 97-0197GLP Nx DATE: 10/8/97 DAYS PI: 7

TEST MATERIAL: Polypropylene SPECIES: Rat L.E. SEX: Female

SPECIMEN: Gluteal Muscle SACRIFICED: CO2

Animal #	Location	Sample #	Macroscopic Observations	D
K-197-01	Left	1	N / N	✓
	Right	2	N / N	✓
K-197-02	Left	1	N / N	✓
	Right	2	N / N	✓
K-197-03	Left	1	N / N	✓
	Right	2	N / N	✓
K-197-04	Left	1	N / N	✓
	Right	2	N / N	✓
K-197-05	Left	1	N / N	✓
	Right	2	N / N	✓

Note: Only one site observed, only one observation necessary, this may not be in study. [initials] 1/12/98

KEY: D = Disposition N = No Abnormality Detected ✓ = Collected

[initials] 11/14/97

Prosector(s) Patricia Inzza Date 10/8/97

HISTOLOGY COMMENTS

Trimming: (All tissues present) Not Present	Embedding: No. Blocks 10	Quality Control: All tissues present Not Present
Other (specify): K-197-01 R site visible?	Other (specify):	Other (specify): Not quality controlled, this may not be in study.
Trimmed By: Pat Inzza Date: 10/13/97	Embedded By: Pat Inzza Date: 10/14/97	Sign Off: [initials] 1/12/98 Date:

CONFIDENTIAL
SUBJECT TO STIPULATION AND ORDER OF CONFIDENTIALITY

Attachment 2

NECROPSY AND TRIM RECORD

PSE ACC#: 97-0197 GLP
Nx DATE: 10/9/97
DAYS PI: 7
TEST MATERIAL: Polypropylene Mesh
SPECIES: Rat L.E
SEX: Female
SPECIMEN: Gluteal Muscle
SACRIFICED: CO2

Animal #	Location	Sample #	Macroscopic Observations	D
K-197-06	Left	1	N	✓
	Right	2	N	✓
K-197-07	Left	1	N	✓
	Right	2	N	✓
K-197-09 (MC 10/9/97)	Left	1	N	✓
	Right	2	N	✓
K-197-10	Left	1	N	✓
	Right	2	N	✓
	Left	1		X
	Right	2		X

Note: Only gross observed, only one observation necessary. No impact on study. DB 1/12/98

DB 1/12/98 ①

KEY: D = Disposition N = No Abnormality Detected ✓ = Collected

DB 11/14/97

Prosector(s) Re-entry for prosector DB 1/12/98 ⑥ Date

HISTOLOGY COMMENTS

Trimming: All tissues present (circled) / Not Present	Embedding: No. Blocks 8	Quality Control: All tissues present / Not Present
Other (specify):	Other (specify):	Other (specify): Not quality controlled. No impact on study. DB 1/12/98
Trimmed By: Pat Ingram	Embedded By: Pat Ingram	Sign Off:
Date: 10/13/97	Date: 10/14/97	Date:

NECROPSY AND TRIM RECORD

PSE ACC# 97-0197 | Nx DATE: 10/15/97 | DAYS PI: 14 Days

TEST MATERIAL: Polypropylene Mesh | SPECIES: LE Rat | SEX: Female

SPECIMEN: Gluteal Muscle | SACRIFICED: CO2

Animal #	Location	Sample #	Macroscopic Observations	D
K-197-11	Left	1	N / N ③ N 11/13/97	✓
	Right	2	N / N ③ N 11/13/97	✓
K-197-12	Left	1	N / N ③ N 11/13/97	✓
	Right	2	N / N ③ N 11/13/97	✓
K-197-13	Left	1	N / N ③ N 11/13/97	✓
	Right	2	N / N ③ N 11/13/97	✓
K-197-14	Left	1	N / N ③ N 11/13/97	✓
	Right	2	N / N ③ N 11/13/97	✓
K-197-15	Left	1	N / N ③ N 11/13/97	✓
	Right	2	N / N ③ N 11/13/97	✓

DJS 11/14/97 KEY: D = Disposition N = No Abnormality Detected ✓ = Collected DJS 10/15/97

Prosector(s) Nancy Trenton Date 10/15/97

HISTOLOGY COMMENTS

Trimming: (All tissues present) Not Present

Embedding: No. Blocks 10

Quality Control: (All tissues present) Not Present

Other (specify): All sites present

Other (specify):

Other (specify):

Trimmed By: Pat Frazza Date: 10/28/97 DD

Embedded By: Pat Frazza Date: 10/29/97 DD

Sign Off: Pat Frazza Date: 11/1/97 DD

NECROPSY AND TRIM RECORD

~~PSE ACC# 97-0197~~ ~~Nx DATE: 10/16/97~~ ~~DAYS PI: 14 Days~~

TEST MATERIAL: Polypropylene Mesh SPECIES: LE Rat SEX: Female

SPECIMEN: Gluteal Muscle SACRIFICED: CO2

Animal #	Location	Sample #	Macroscopic Observations	D
K-197-16	Left	1	N ~~N~~ ③ NT 11/13/97	✓
	Right	2	N ~~N~~ ③ NT 11/13/97	✓
K-197-17	Left	1	N ~~N~~ ③ NT 11/13/97	✓
	Right	2	N ~~N~~ ③ NT 11/13/97	✓
K-197-18	Left	1	N ~~N~~ ③ NT 11/13/97	✓
	Right	2	N ~~N~~ ③ NT 11/13/97	✓
K-197-19	Left	1	N ~~N~~ ③ NT 11/13/97	✓
	Right	2	N ~~N~~ ③ NT 11/13/97	✓
K-197-20	Left	1	N ~~N~~ ③ NT 11/13/97	✓
	Right	2	N ~~N~~ ③ NT 11/13/97	✓

23 11/14/97

KEY: D = Disposition N = No Abnormality Detected ✓ = Collected

Prosector(s) Nancy Irenton Date 10/16/97

HISTOLOGY COMMENTS

Trimming: (All tissues present) Not Present	Embedding: No. Blocks 10	Quality Control: (All tissues present) Not Present
Other (specify): (Ablate) ③ present	Other (specify):	Other (specify):
Trimmed By: Pat Frazer Date: 10/28/97	Embedded By: Pat Frazer Date: 10/29/97	Sign Off: Pat Frazer Date: 11/1/97

Attachment 2

NECROPSY AND TRIM RECORD

PSE ACC#: 97-0197 GLP Nx DATE: 10/29/97 DAYS PI: 28

TEST MATERIAL: Polypropylene Mesh SPECIES: Rat L.E. SEX: Female

SPECIMEN: Gluteal Muscle SACRIFICED: CO2

Animal #	Location	Sample #	Macroscopic Observations	D
K-197-21	Left	1	N	✓
	Right	2	N	✓
K-197-22	Left	1	N	✓
	Right	2	N	✓
K-197-23	Left	1	N	✓
	Right	2	N	✓
K-197-24	Left	1	N	✓
	Right	2	N	✓
K-197-25	Left	1	N	✓
	Right	2	N	✓

DJB 11/14/97 KEY: D = Disposition, N = No Abnormality Detected ✓ = Collected

Prosector(s) Patricia Frazer Date 10/29/97

HISTOLOGY COMMENTS

Trimming: All tissues present
Not Present
No comments written
Other (specify): DJB 1/12/98

Embedding:
No. Blocks 10
Other (specify):

Quality Control: All tissues present
Not Present
No QC notation.
Other (specify): DJB 1/12/98

Trimmed By: Pat Frazer Date: 11/10/97

Embedded By: Pat Frazer Date: 11/11/97

Sign Off: Pat Frazer Date: 11/13/97

Attachment 2

NECROPSY AND TRIM RECORD

PSE ACC#: 97-0197 GLP   Nx DATE: 10/30/97   DAYS PI: 28

TEST MATERIAL: Polypropylene Mesh   SPECIES: Rat L.E   SEX: Female

SPECIMEN: Gluteal Muscle   SACRIFICED: CO2

Animal #	Location	Sample #	Macroscopic Observations	D
K-197-26	Left	1	N	✓
	Right	2	N	✓
K-197-27	Left	1	N	✓
	Right	2	N	✓
K-197-28	Left	1	N	✓
	Right	2	N	✓
K-197-29	Left	1	N	✓
	Right	2	N	✓
K-197-30	Left	1	N	✓
	Right	2	N	✓

KEY: D = Disposition N = No Abnormality Detected ✓ = Collected

11/4/97

Prosector(s) Pat Inzza   Date 10/30/97

HISTOLOGY COMMENTS

Trimming: All tissues present (circled) / Not Present

Embedding: No. Blocks 10

Quality Control: All tissues present (circled) / Not Present

Other (specify):

Other (specify):

Other (specify):

Trimmed By: Pat Inzza   Date: 11/10/97

Embedded By: Pat Inzza   Date: 11/11/97

Sign Off: Pat Inzza   Date: 11/13/97

TEST ARTICLE USAGE LOG

TEST/CONTROL ARTICLE: Ulmsten Polypropylene Mesh	**LOT NO.:** EB1
STORAGE CONDITIONS: AMB/AMB	**DATE REC'D:** 9/10/97
DESCRIPTION/SIZE: Polypropylene mesh from the Ulmsten Device	**NUMBER OF PACKAGES INITIALLY REC'D:** 5

ACCESSION NO.	AMT RELEASE (-)/AMT RETURNED (+)	NO. PKGS. REMAINING	DATE	INITIALS
K5463	-1 to analytical for baseline characterization	4	9/22/97	NT
K5391	-1 ~~ui~~ non-glp characterization	3	9/23/97	NT
97-0197	-1 implantation	2	10/1/97	NT
97-0197	-1 implantation	1	10/2/97	NT
	-1 ~~destroyed~~ ①NT 1/9/98 returned to Cary Linsky	0	1/9/98	NT

P:\DRGFRM.WP

TEST ARTICLE USAGE LOG

TEST/CONTROL ARTICLE: PROLENE Polypropylene Mesh	LOT NO.: JJ2009
STORAGE CONDITIONS: AMB/AMB	DATE REC'D: 9/11/97
DESCRIPTION/SIZE: 6" x 6" Product Code - PM-M EXP JUL 01 Nonabsorbable synthetic Surgical mesh	NUMBER OF PACKAGES INITIALLY REC'D: 3

ACCESSION NO.	AMT RELEASE (-)/AMT RETURNED (+)	NO. PKGS. REMAINING	DATE	INITIALS
K5464	-1 to analytical for baseline characterization	2	9/22/97	NT
K5391	-1 for non-glp characterization	1	9/23/97	NT
97-0197	-1 for implantation	0	10/1/97	NT

P:\DRGFRM.WP

ETHICON, INC.
a Johnson & Johnson company

P.O. BOX 151
SOMERVILLE, NEW JERSEY 08876-0151

To: GLP Archivist
From: [signature] for Dr. R. Hutchinson
Date: August 10, 1999

Subject: Supplemental Information
Accession No.: 97-0197

Please add the following supplemental information to the previously archived study file.

Type of Data	Total # Pages
Histology Record	02
Special Histology Request Forms	03
Total	05

PATHOLOGY, TOXICOLOGY & SURGERY - HISTOLOGY RECORD

PTS ACCESSION NO. 97-0197 MATERIAL [illegible] SPECIES Rat

DAYS PI	ANIMAL NO(S)	NO. BLOCKS	SECTIONING DATE	SECTIONING INIT	STAINING DATE	STAINING INIT	NO. SLIDES	COMMENTS L+R
7	*K-197-01 K-197-02	4	11/3/97	P.T	11/5/97	P.T	4+1	1L RECUT A 1 sl 11/10/97
7	*K-197-03 K-197-04	4+1	11/3/97	P.T	11/5/97	P.T	4+1	3L RECUT A 1 sl 12/8/97 4L RECUT A 1 sl 11/10/97 +1 3LA, 4LA 2 sl. 12/5/97 2 sl. 12/5/97 12/8/97
7	K-197-05	2	11/3/97	P.T	11/5/97	P.T	2	
7	K-197-06 *K-197-07	4	11/3/97	P.T	11/5/97	P.T	4+1	7L RECUT A 1 sl 11/10/97
7	*K-197-09	2+1	11/3/97	P.T	11/5/97	P.T	2+1	9R RECUT A 1 sl 11/10/97 9RLA 1 sl. 12/5/97 12/8/97 1 sl 12/5/97
7	K-197-10	2	11/3/97	P.T.	11/5/97	P.T	2	
14	K-197-11 *K-197-12	4+2	11/7/97	P.T	11/7/97	P.T	4+1	12R RECUT A 11RA, 12RA 2 sl 12/5/97 12/8/97 2 sl. 12/5/97
14	*K-197-13 K-197-14	4+1	11/7/97	P.T	11/7/97	P.T	4+1	13R RECUT A 12/8/97 13RA 1 sl 12/5/97 1 sl. 12/5/97
14	K-197-15	2	11/7/97	P.T.	11/7/97	P.T	2	

General Comments:

Re-cuts = (R), Staining other than H&E = (TC) Trichrome, all others = (SS)

Slide Filing Record: Date of initial filing of completed study:________

Slide No(s) Removed (date/initials) Returned (date/initials)

Pg 1 of 5 [illegible] 8/3/99

PATHOLOGY, TOXICOLOGY & SURGERY - HISTOLOGY RECORD

PTS ACCESSION NO. 97-0197 MATERIAL Polypropylene SPECIES Rat L.E

DAYS PI	ANIMAL NO(S)	NO. BLOCKS	SECTIONING DATE	SECTIONING INIT	STAINING DATE	STAINING INIT	NO. SLIDES	COMMENTS L+R H+E
14	K-197-16 K-197-17	4	11/10/97	P.T	11/11/97	P.T	4	
14	K-197-18 K-197-19	4	11/10/97	P.T	11/11/97	P.T	4	
14	K-197-20	2	11/10/97	P.T	11/11/97	P.T	2	
28	K-197-21 K-197-22	4	11/12/97	P.T	11/13/97	P.T	4	(1) (1)
28	K-197-23 K-197-24	4+1	11/12/97	P.T	11/13/97	P.T	4	23 LA 1 bl 12/5/97 1 sl 12/5/97 12/8/97
28	K-197-25	2	11/12/97	P.T.	11/13/97	P.T	2	(1)
28	K-197-26 K-197-27	4+1	11/12/97	P.T	11/13/97	P.T	4	27 LA 1 bl. 12/5/97 1 sl. 12/5/97 12/8/97
28	K-197-28 K-197-29	4	11/12/97	P.T	11/13/97	P.T	4	
28	K-197-30	2+1	11/12/97	P.T	11/13/97	P.T	2	30 LA 1 bl. 12/5/97 1 sl 12/5/97 12/8/97

General Comments:

Re-cuts = (R), Staining other than H&E = (TC) Trichrome, all others = (SS)

Slide Filing Record: Date of initial filing of completed study:__________

Slide No(s) Removed (date/initials) Returned (date/initials)

~~(1) per Pat Jorgan note An #21, 22, 25 had blocks prepared but no slides~~ RE RRL 8/3/99

Pg 2 of 5 RRL 8/3/99

PTS SOP NO. 10

APPENDIX 6

PATHOLOGY, TOXICOLOGY & SURGERY

REQUEST FOR SPECIAL HISTOLOGY

THIS SECTION TO BE FILLED OUT BY THE REQUESTOR	
REQUESTOR: D. Bartlett	
ACCESSION NO.: 97-0197	ANIMAL NO(S).: 01, 03, 04, 07, 09
SLIDE(S)/BLOCK(B) NO(S).: 01L, 03L, 04L, 07L, 09R	
ORGAN OR TISSUE: Implant site	
STAIN OR PROCEDURE REQUIRED: H+E, [illegible]	
DATE SUBMITTED: 11/1/97	DATE NEEDED: 11/13/97

THIS SECTION TO BE FILLED OUT BY HISTOLOGY LAB	
ASSIGNED TO: P.T.	
BLOCK NO(S).: 01L, 03L, 04L, 07L, 09R 5 sl total (RECUT A)	
DATE SECTIONED: 11/10/97	DATE STAINED: 11/11/97
DATE DELIVERED: 11/11/97	
RECEIVED BY: T.B.	
COMMENTS: 03L RECUT ONLY ONE SMALL SUTURE PRESENT AT SECTIONING PT.	

histrec4.stb

PS 3 of 5

PTS SOP NO. 10

APPENDIX 6

PATHOLOGY, TOXICOLOGY & SURGERY

REQUEST FOR SPECIAL HISTOLOGY

THIS SECTION TO BE FILLED OUT BY THE REQUESTOR	
REQUESTOR: JBarbolt	
ACCESSION NO.: 97-0197	ANIMAL NO(S).: 12,13
SLIDE(S)/BLOCK(B) NO(S).: 12R, 13R	
ORGAN OR TISSUE: Implantation site	
STAIN OR PROCEDURE REQUIRED: H&E - cut deeper	
DATE SUBMITTED: 11/14/97	DATE NEEDED: 11/21/97

THIS SECTION TO BE FILLED OUT BY HISTOLOGY LAB	
ASSIGNED TO: P.T.	
BLOCK NO(S).: 12R, 13R Recut A	2 sl. total
DATE SECTIONED: 12/1/97	DATE STAINED: 12/2/97 PT
DATE DELIVERED: 12/3/97	
RECEIVED BY: T.B.	
COMMENTS:	

histrec4.stb

B4015

PTS SOP NO. 10

APPENDIX 6

PATHOLOGY, TOXICOLOGY & SURGERY

REQUEST FOR SPECIAL HISTOLOGY

THIS SECTION TO BE FILLED OUT BY THE REQUESTOR	
REQUESTOR: D Bartlett	
ACCESSION NO.: 97-0197	ANIMAL NO(S).: 03, 04, 09, 11, 12, 13, 23, 27, 30
SLIDE(S)/BLOCK(B) NO(S).: 03L, 04L, 09R, 11R, 12R, 13R, 23R, 27L, 30L	
ORGAN OR TISSUE: Implantation sites	
STAIN OR PROCEDURE REQUIRED: Retrim from wet tissue, H&E	
DATE SUBMITTED: 11/14/97	DATE NEEDED: 11/21/97

THIS SECTION TO BE FILLED OUT BY HISTOLOGY LAB	
ASSIGNED TO: AT	
BLOCK NO(S).: RETRIMMED WET TISSUE 03L, 04L, 09R, 11R, 12R, 13R, 23R, 27L, 30L 9 total	9bl.
DATE SECTIONED: 12/5/97	DATE STAINED: 12/8/97
DATE DELIVERED: 12/8/97	
RECEIVED BY: TB	
COMMENTS:	

histrec4.stb

PS 50/5

ETH.MESH.05315295

EXHIBT A-2

The Science of
"What's Left Behind"…
Evidence & Follow-Up of Mesh Use for SUI

Nick Franco, MD
Naples, FL

This promotional educational activity is brought to you by Ethicon, Inc. and is *not* certified for continuing medical education.

Navigating the Mesh Maze

- How do I deal with the competing messages surrounding mesh?
- Goal is safe and effective treatment for patients with SUI
- FDA has issued a PHN warning about risks of mesh
- Patients are concerned about mesh implant
- How do I minimize my risk?

HIGHLY CONFIDENTIAL
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FDA Public Health Notification: 10/20/08

"Serious Complications with Mesh Use in PFR and SUI Repair"[1]

>1,000 complications encompassing 9 mesh manufacturers reported in past 3 years

FDA Recommendations:

- Obtain specialized training, be aware of risks
- Be vigilant for potential adverse events (erosion, infection)
- Watch for perforations from tools
- Inform patients that mesh implantation is permanent, and that some complications may require additional surgery that may or may not correct the complication
- Inform patients about potential for serious complications effecting QOL (dyspareunia, scarring)
- Provide patients with a written copy of the patient labeling

HIGHLY CONFIDENTIAL
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Implications of FDA PHN

- We should be counseling patients differently about mesh
- When selecting a sling, "what's left behind" matters more than the delivery system
- Meshes are different and should be assessed by their own clinical outcomes
- In a category such as slings where "Level I Evidence" exists with proven safety and efficacy, why accept a mesh without outcomes data

HIGHLY CONFIDENTIAL
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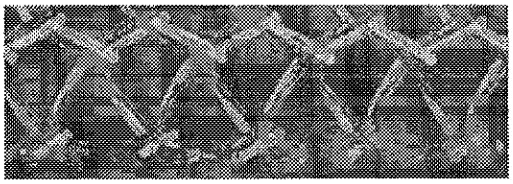
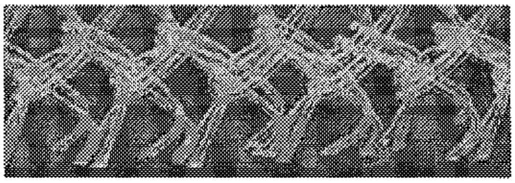
All Meshes are NOT Equal

Macroscopic Images of Mesh Samples

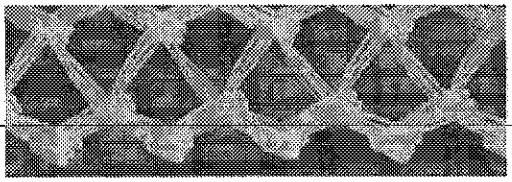
All are polypropylene. . .but meshes have differences



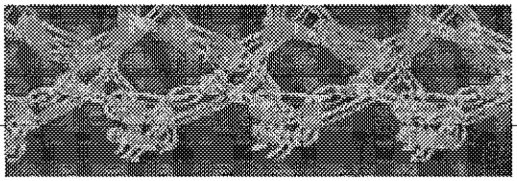
ETHICON
Women's Health & Urology



AMS
(without tensioning suture)



BOSTON SCIENTIFIC



BARD

What are the mechanical properties of an ideal sling design?

- Incorporates into tissue
- Not stiff to risk causing erosions, voiding dysfunction or urethral obstruction
- Ability to elongate and mimic natural tissue
- Inert and doesn't potentiate infection

Textile Property Comparison of Various Polypropylene Meshes[2]

Mesh type	Ethicon Women's Health & Urology	AMS	Boston Scientific	Bard
Tissue In-Growth				
Pore size	1379 µm	1000 µm	1182 µm	1160 µm
Erosions? Voiding Dysfunction?				
Low stiffness (N/mm)	0.09±0.01	0.09±0.03*	0.58±0.15	0.16±0.07
Mimic natural tissue				
Relative elongation at inflection point (%)	71.2±2.5	66.4±6.1	20.1±3.4	38.3±9.5

*AMS mesh was tested without the tensioning suture.[2] In another study comparison when measured with the tensioning suture SPARC™ has a stiffness of 0.53 N/mm and GYNECARE TVT™ Tension-free Support for Incontinence has a stiffness of 0.23 N/mm. This is a highly significant difference (*P*=.001).[3]

GYNECARE TVT™ Tension-free Support for Incontinence Mesh

Unique Properties

- Measurable differences from other polypropylene meshes[2]
  - Largest pore size[2]
  - Lowest stiffness[2]
  - Highest elongation[2]

GYNECARE TVT™ Family of Products
Tension-free Support for Incontinence Timeline

- Developed through meticulous design
  - "Intravaginal Slingplasty Study" evaluated various implant materials
  - Prolene* Polypropylene Mesh selected for sling
    - Used in Ethicon Products Sutures since 1969
- Product advancement without device recall
- Proven efficacy and safety

1993-1996 Ulmsten develops **GYNECARE TVT™ Retropubic System Tension-free Support for Incontinence**

1997 **GYNECARE TVT™ Retropubic System Tension-free Support for Incontinence** launches

2004 **GYNECARE TVT™ Obturator System Tension-free Support for Incontinence launches**

X X

2006 **GYNECARE TVT SECUR™ System Tension-free Support for Incontinence launches**

*Trademark

X X Other brand slings taken off market

"Level I Evidence" Overview

Mesh type	Ethicon Women's Health & Urology	AMS	Boston Scientific	Bard
RCTs	41	11	0	0

Date of study: 1/26/09 - 2/20/09

GYNECARE TVT™ Family of Products Tension-free Support for Incontinence Data Overview

- GYNECARE TVT™ Retropubic System Tension-free Support for Incontinence
  - 11.5 year follow-up: 97.0% success rate[4]

- GYNECARE TVT™ Obturator System Tension-free Support for Incontinence
  - 3 year follow-up: 96.7% success rate[5]

- GYNECARE TVT SECUR® System Tension-free Support for Incontinence
  - WW Registry 12-month follow-up of 253 patients
    - **Presentation Time:** Tuesday, April 28; 11:10-11:20
    - **Presentation Number:** 1520
    - **Podium:** 37

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GYNECARE TVT™ Tension-free Support for Incontinence Mesh Summary

- Prolene* Polypropylene Mesh is highly inert
- Treated over 1.5 million patients[6]
- Longest term follow-up of any mesh at 11.5 years[4]
- The most "Level I Evidence" with 41 RCTs[7]

*Trademark

Questions?

REFERENCES

[1]FDA Public Health Notification: http://www.fda/gov/cdrh/safety/102008-surgicalmesh.html.

[2]Moalli P, Papas N, Menefee S, Albo M, Meyn L, Abramowitch S.Tensile properties of five commonly used mid-urethral slings relative to the TVT™. *Int Urogynecol J.* 2008;19:665-663.

[3]Dietz H, Vancaillie P, Svehla M, Walsh W, Steensma A, Vancaillie T. Mechanical properties of urogynecologic implant materials. *Int Urogynecol J.* 2003;14:239–243.

[4]Nilsson C G, Palva K, Rezapour M, Falconer C. Eleven Years Prospective Follow-Up of the Tensions-Free Vaginal Tape Procedure for Treatment of Stress Urinary Incontinence. *Int Urogynecol J.* 2008;19:1043-1047.

[5]Waltregny D, Gaspar Y, Reul O, Hamida W, Bonnet P, de Leval J. TVT-O for the Treatment of Female Stress Urinary Incontinence: Results of a Prospective Study after a 3-Year Minimum Follow-Up. *Eur Urol.* 2007;53:401-410.*Int Urogyencol J.* 2005;16:230-235.

[6]Data on file based on units sold, Ethicon, Inc.

[7]Pubmed search from 1/26/09- 2/20/09 using limitation of "English" and individual terms "TVT", "SPARC", "Advantage", "AdvantageFit", "Align", "Uretex", "Aris", "TVT Obturator", "Monarc", "Obtryx", "Align TO", "Uretex TO", "Aris TO", "Desara", "Lynx", "TVT SECUR", "Miniarc", "Solyx", "Prefyx PPS", "Contasure", "Ajust", "T-Sling", "Needleless", "Minitape", all with the following terms "female", "incontinence". Handsearching of conference proceedings and searching of reference lists.
[7]http://phpartners.org/tutorial/04-ebph/2-keyConcepts/4.2.7.html.

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GYNECARE TVT™ FAMILY OF PRODUCTS
ESSENTIAL PRODUCT INFORMATION

INDICATIONS

The GYNECARE TVT™ Family of Products: GYNECARE TVT SECUR®, GYNECARE TVT™, GYNECARE TVT with Abdominal Guides, and GYNECARE TVT™ Obturator System are intended to be used in women as suburethral slings for the treatment of stress urinary incontinence (SUI).

CONTRAINDICATIONS

As with any suspension surgery, these procedures should not be performed in pregnant patients.

Additionally, because the PROLENE™ polypropylene mesh will not stretch significantly, it should not be performed in patients with future growth potential including women with plans for future pregnancy.

WARNINGS & PRECAUTIONS

- Do not use the GYNECARE TVT Family of Products for patients who are on anti-coagulation therapy.
- Do not use the GYNECARE TVT Family of Products, for patients who have a urinary tract infection.
- Bleeding or infection may occur post-operatively.
- Transient leg pain lasting 24-48 hours may occur and can usually be managed with mild analgesics after a GYNECARE TVT Obturator System.
- Since no clinical information is available about pregnancy following sub-urethral sling procedure with the GYNECARE TVT Family of Products, the patient should be counseled that future pregnancy may negate the effects of the surgical procedure and the patient may again become incontinent.
- Since no clinical information is available about vaginal delivery following sub-urethral sling procedure with the GYNECARE TVT Family of Products, in case of pregnancy, delivery via cesarean section should be considered.
- Post-operatively, refrain from heavy lifting and/or exercise (e.g. cycling, jogging) for at least three to four weeks and to refrain from intercourse for one month. The patients can usually return to other normal activity after one or two weeks.
- Contact your surgeon immediately if there is burning sensation during urination, unusual bleeding, problems voiding or other problems.

ADVERSE REACTIONS

- Punctures or lacerations or injury to vessels, nerves, bladder, urethra, or bowel may occur during instrument passage and may require surgical repair.
- Improper placement of the TVT device may result in incomplete or no relief from urinary incontinence or may cause urinary tract obstruction.
- Transitory local irritation at the wound site and a transitory foreign body response may occur. This could result in extrusion, erosion, fistula formation or inflammation.

For more information, please consult your doctor or call 1-888-GYNECARE to speak with a nurse.

ETHICON Women's Health & Urology, a division of Ethicon, Inc., a JOHNSON & JOHNSON company

Thank You

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CR Approved 4-15-09

EXHIBT A-3

GYNECARE TVT Tension-free Support for Incontinence

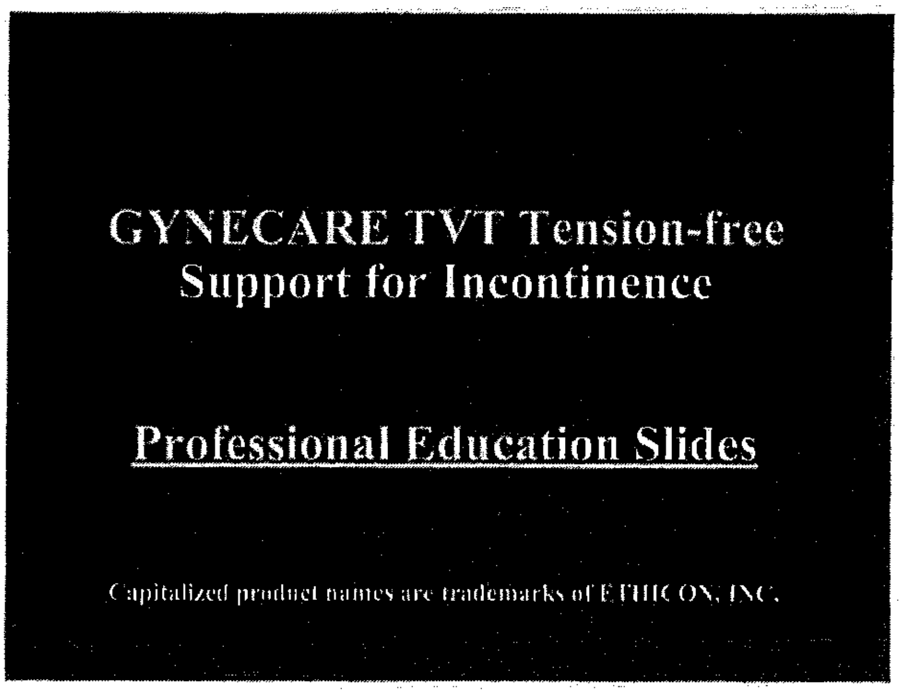

GYNECARE TVT Tension-free
Support for Incontinence
Professional Education Slides
Capitalized product names are trademarks of ETHICON, INC.

EXHIBIT
T-792
7/11/13 SPW
PENGAD 800-631-6989

GYNECARE TVT Tension-free Support for Incontinence

Pathophysiology of Genuine Stress Urinary Incontinence

I. Defects in the support structure
   A. Pubourethral ligaments (mid-urethra)
   B. Suburethral vaginal hammock (a.k.a. endopelvic fascia) at the urethrovesical junction
   C. Connective tissue (collagen fibers) interconnecting the above structures
   D. Levator ani muscles - tone/contractility

II. Defects in both intrinsic and extrinsic urethral function:
   A. Denervation
   B. Devascularization
   C. Aging
   D. Trauma

GYNECARE TVT Tension-free Support for Incontinence

Choice of Surgery Based on Cause

Hypermobility	ISD	Both
1. Abdominal RPU	1. Injections	1. Slings
2. Needle urethropexies	2. Slings	
3. Slings		

GYNECARE TVT Tension-free Support for Incontinence

Goal of Surgery

1. Restore and/or reinforce the pubourethral ligaments at the mid-urethra.
2. Restore and/or reinforce the suburethral vaginal hammock at the mid-urethra.
3. Reinforce the paraurethral connective tissue.

Although classically it has been taught that the goal of surgery is to restore the anatomy of the bladder neck to its correct anatomical position, this treatment is only helpful for the hypermobility aspect of the incontinence. It is now generally recognized that many patients with hypermobility also have some Intrinsic Sphincter Deficiency (ISD), which is not addressed with correction of the bladder neck anatomy. By restoring and reinforcing the pubourethral ligaments and suburethral vaginal hammock at the mid-urethral level, patients with both hypermobility and ISD can be effectively treated. Additionally, in patients with only a hypermobility component to their incontinence, mid-urethral support has been shown to be effective using GYNECARE TVT tension-free support.

GYNECARE TVT Tension-free Support for Incontinence

GYNECARE TVT Tension-free Support for Incontinence

GYNECARE TVT Tension-free Support for Incontinence is intended to be used as a pubourethral sling for treatment of Stress Urinary Incontinence (SUI), for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency (ISD).

GYNECARE TVT Tension-free Support for Incontinence

History of GYNECARE TVT

Tension-free Support for Incontinence

GYNECARE TVT Tension-free Support for Incontinence

History of GYNECARE TVT Tension-free Support

- Based on Integral theory set forth by Petros and Ulmsten*
  - Proposes that control of the urethra closure is mainly the interplay of 3 structures
    - pubourethral ligaments
    - suburethral vaginal hammock
    - pubococcygeus muscle

*An integral theory of female urinary incontinence. Experimental and clinical consideration. *Acta Obstet Gynecol Scand* 1990:7-31 (Suppl 153).

A differing theory on the mechanisms of incontinence comes from Robert Rogers MD, who postulates that there are actually six mechanisms of urinary incontinence including:

1) Involuntary smooth muscles of the internal sphincter

2) Voluntary striated muscles of the external sphincter

3) Submucosal coaptation of the urethra

4) Endopelvic fascial support

5) Compliance of the bladder

6) A "kinking" of the mid-urethra as a result of the pubourethral ligaments in combination with hypermobility of the bladder neck.

GYNECARE TVT Tension-free Support for Incontinence

History of GYNECARE TVT Tension-free Support

- First published in *Scand J Urol Nephrol* 1995 as an intravaginal slingplasty
- Descriptive Study of 50 patients
  - 37 Mersilene 5 Gortex
  - 6 Teflon 2 Lyodura
- Technique was slightly different
- Sinus tract in 2 Gortex cases
- 78% dry, 12% improved

GYNECARE TVT Tension-free Support for Incontinence

History of GYNECARE TVT Tension-free Support

- Instrument refinements
  - 1.0 X 40 cm PROLENE mesh covered by plastic sheaths
  - Non-disposable metal handle specifically couples to disposable needles
- Procedure Changes
  - No vaginoplasty
  - Suprapubic incision: one 2 cm two 1 cm
  - Hegar #7 sound used to check urethral lumen after placement of the mesh

GYNECARE TVT Tension-free Support for Incontinence

GYNECARE TVT Tension-free Support for Incontinence

Key Highlights

- PROLENE polypropylene mesh tape
- No fixation, no tension
- Trans-vaginal approach
- Minimal tissue dissection
- Local anesthesia, sedation, regional, general
- Minimally invasive
- Normally, same day discharge
- Normally, no post-op urinary catheterization

The GYNECARE TVT device is similar to the conventional sling devices in that a supportive hammock of PROLENE mesh is placed below and around the urethra. It differs from other sling devices because the PROLENE mesh is placed under the mid-urethra, away from the bladder neck and is placed in a "tension-free" manner. At the mid-urethra, the mesh does not interfere with funneling of the bladder neck that proceeds normal voiding, and as a result post-operative voiding problems are not common. Additionally, the mesh is placed vaginally using minimal tissue dissection and suture fixation is not required.

GYNECARE TVT Tension-free Support for Incontinence

GYNECARE TVT
Patient Selection

The GYNECARE TVT Tension-free Support for Incontinence device is appropriate for the following:

- Primary and secondary cases of SUI
- Hypermobile urethra
- Low pressure urethra (ISD – type III)
- Stress urinary incontinence with concomitant prolapse such as:
  - Anterior wall insufficiency
  - Posterior wall insufficiency
  - Vaginal vault prolapse
- Obese and elderly patients

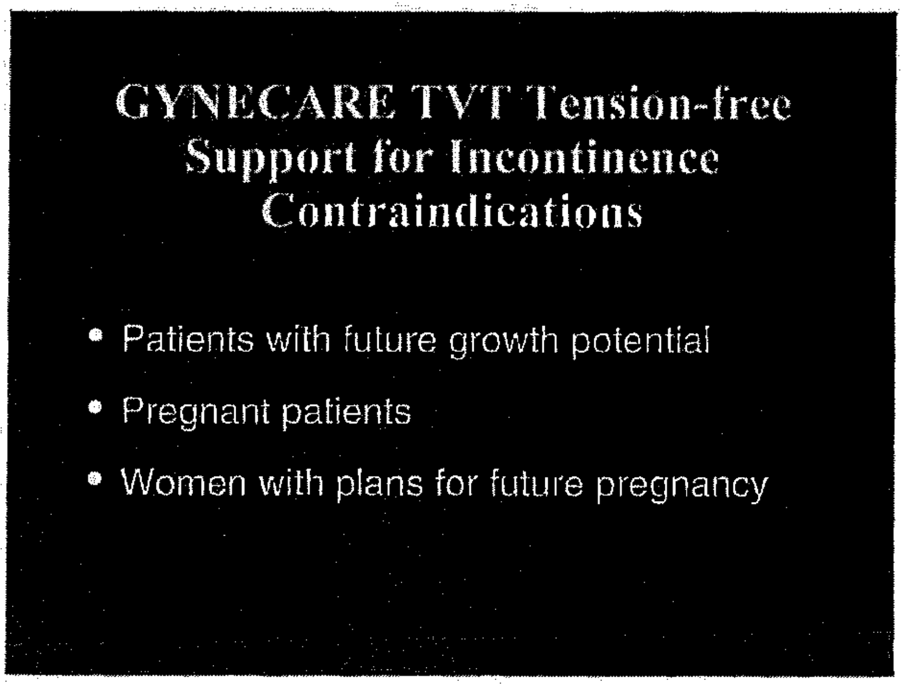
GYNECARE TVT Tension-free Support for Incontinence

GYNECARE TVT Tension-free Support for Incontinence Indications

- Indicated for treatment of Female Stress Urinary Incontinence resulting from:
  - urethral hypermobility and/or
  - intrinsic sphincter deficiency

Please review the complete package insert included in the Preceptee Binder.

GYNECARE TVT Tension-free Support for Incontinence


GYNECARE TVT Tension-free
Support for Incontinence
Contraindications
• Patients with future growth potential
• Pregnant patients
• Women with plans for future pregnancy

Please review the complete package insert, which is included in the Preceptee Binder.

An example of patients with future growth potential would be adolescent patients.

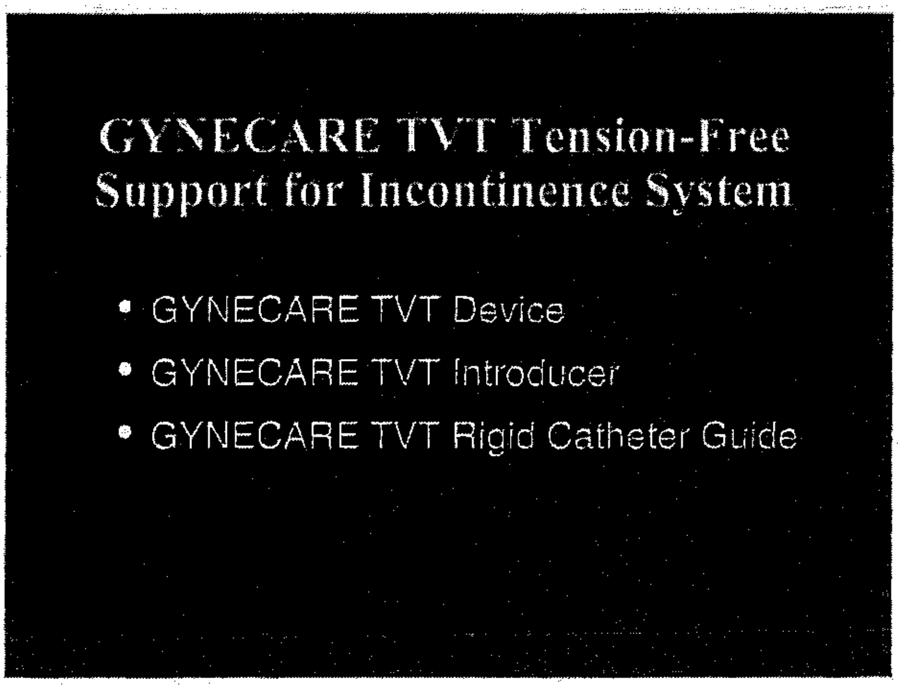
GYNECARE TVT Tension-free Support for Incontinence

Warnings and Precautions

- Do not use GYNECARE TVT Device for patients who are on anticoagulation therapy.
- Do not use GYNECARE TVT Device for patients who have a urinary tract infection.
- Users should be familiar with surgical techniques for bladder neck suspensions before employing the GYNECARE TVT Device. It is, however, important to recognize that GYNECARE TVT Tension-free Support for Incontinence is different from a traditional sling procedure in that the tape should be located without tension under midurethra.
- Acceptable surgical practice should be followed for the GYNECARE TVT Device as well as for the management of contaminated or infected wounds.
- Incontinence repair using the GYNECARE TVT Device should be performed with care to avoid large vessels, nerves, bladder, and bowel. Attention to local anatomy and proper passage of the needles will minimize risks.
- Retropubic bleeding may occur postoperatively. Observe for any symptoms of signs before releasing the patient from the hospital.
- Cystoscopy should be performed to confirm bladder integrity or recognize a bladder perforation.
- The GYNECARE TVT Rigid Catheter Guide should be gently pushed into the Foley catheter so that the GYNECARE TVT Rigid Catheter Guide does not extend into the holes of the Foley catheter.
- When removing the GYNECARE TVT Rigid Catheter Guide, open the handle completely so that the catheter remains properly in place.
- Do not remove the plastic sheath until the tape has been properly positioned.
- Ensure that the tape is placed with minimal tension under midurethra
- PROLENE mesh in contaminated areas should be used with the understanding that subsequent infection may require removal of the material.
- The patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent.

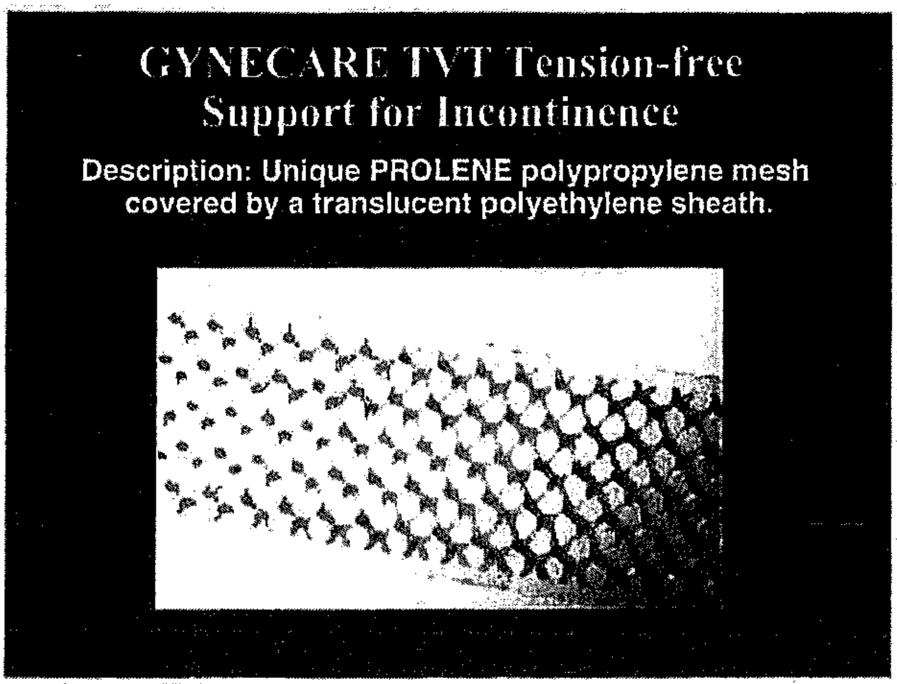
Advise Preceptee to review complete package insert prior to performing the procedure.

GYNECARE TVT Tension-free Support for Incontinence


GYNECARE TVT Tension-Free Support for Incontinence System
• GYNECARE TVT Device
• GYNECARE TVT Introducer
• GYNECARE TVT Rigid Catheter Guide

The GYNECARE TVT Device consists of a PROLENE polypropylene mesh tape that is covered with a plastic sheath and attached to two stainless steel introducer needles. The device, when used in conjunction with the TVT Introducer and TVT Rigid Catheter Guide, make up the GYNECARE TVT System.

GYNECARE TVT Tension-free Support for Incontinence


GYNECARE TVT Tension-free
Support for Incontinence
Description: Unique PROLENE polypropylene mesh
covered by a translucent polyethylene sheath.

The PROLENE mesh tape is encased in a protective plastic sheath which remains in place until insertion. This sheath, and the minimal dissection involved in its placement, minimize the risk of contamination of the tape.

GYNECARE TVT Tension-free Support for Incontinence

PROLENE Mesh Attributes

The PROLENE mesh of GYNECARE TVT tension-free support is different from other polypropylene meshes available in the marketplace, including other forms of PROLENE mesh sold by ETHICON, INC. for general surgery or for hernia repair.

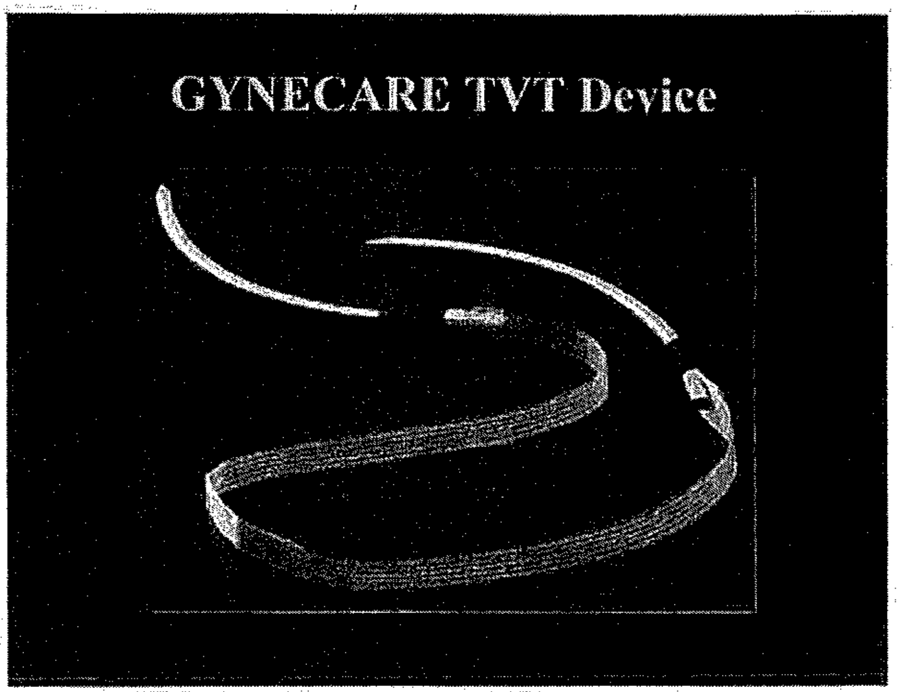
Polymeric materials require the addition of additives in the manufacturing process. The additives in PROLENE are different than those used by other manufacturers. It is well established by the FDA that additives can affect material biocompatibility and other material properties.

Other PROLENE and polypropylene materials also differ from that of GYNECARE TVT mesh in terms of fiber diameter and knit. These differences can affect pore size and associated tissue in-growth, feel of the mesh, and mesh elasticity properties.

GYNECARE TVT PROLENE is the only polypropylene material that has been used in over 150,000 patients world-wide for the treatment of stress incontinence.

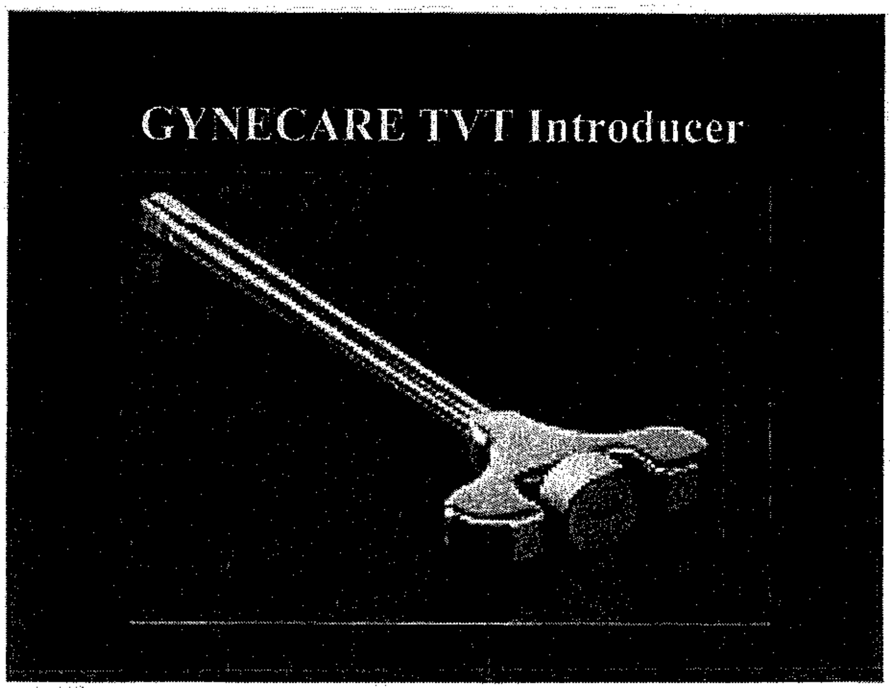
It should be noted that Ulf Ulmsten, MD originally used other mesh materials when developing his technique of placing mesh at the mid-urethra without tension.

GYNECARE TVT Tension-free Support for Incontinence



The protected mesh attached to introducer needles ready for the application.

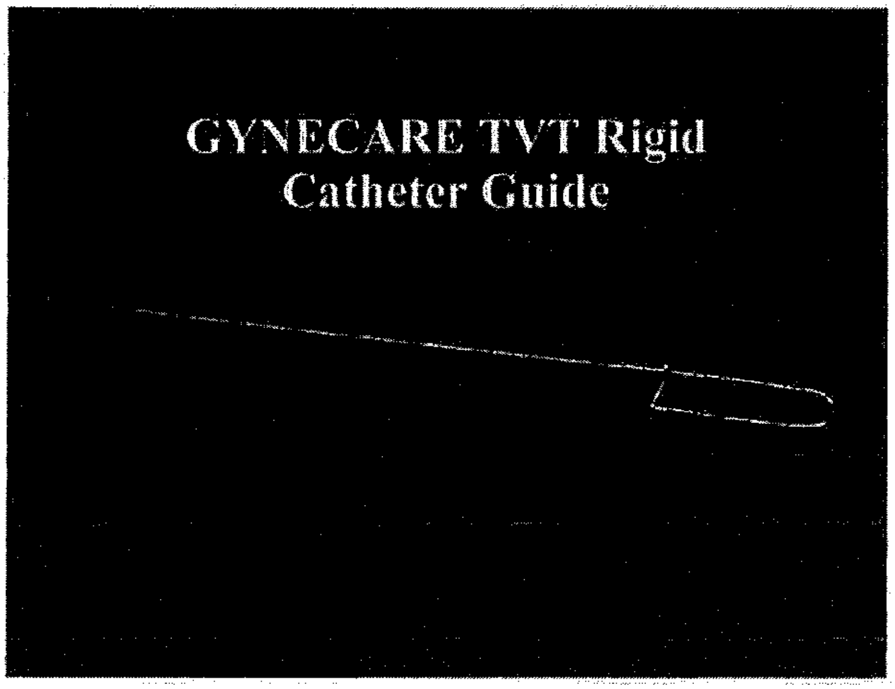
GYNECARE TVT Tension-free Support for Incontinence



The introducer allows accurate and controlled introduction of the needles with the attached tape.

This is a reusable instrument.

GYNECARE TVT Tension-free Support for Incontinence

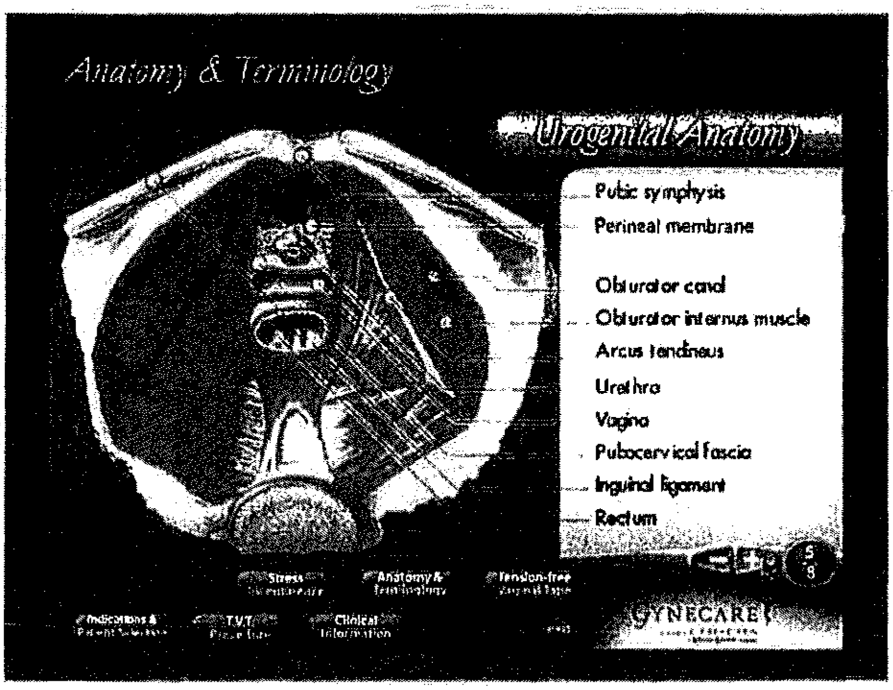


The catheter guide is inserted into an 18 Fr. Foley catheter and the resulting assembly is inserted transurethrally into the bladder. This allows mobilization of the bladder neck and urethra away from the path of the GYNECARE TVT device.

GYNECARE TVT Tension-free Support for Incontinence

Pelvic Anatomy

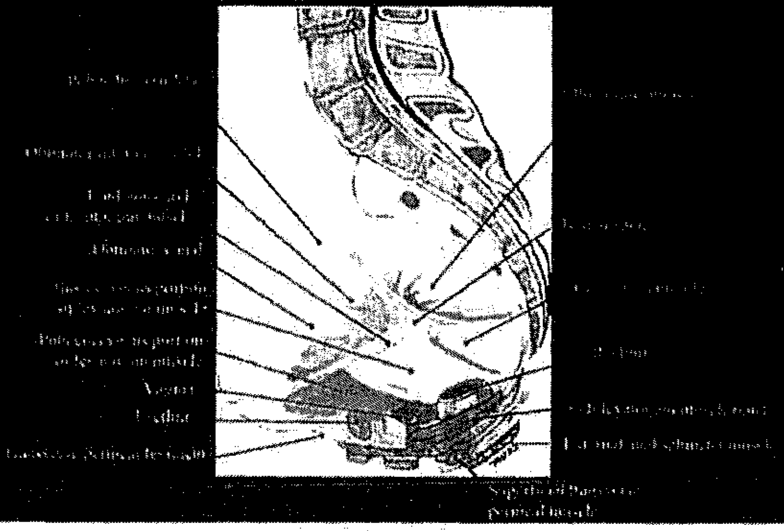
GYNECARE TVT Tension-free Support for Incontinence


Anatomy & Terminology
Urogenital Anatomy
Pubic symphysis
Perineal membrane
Obturator canal
Obturator internus muscle
Arcus tendineus
Urethra
Vagina
Pubocervical fascia
Inguinal ligament
Rectum
Stress
Anatomy & Terminology
Tension-free
Indications &
T.V.T.
Clinical Information
GYNECARE

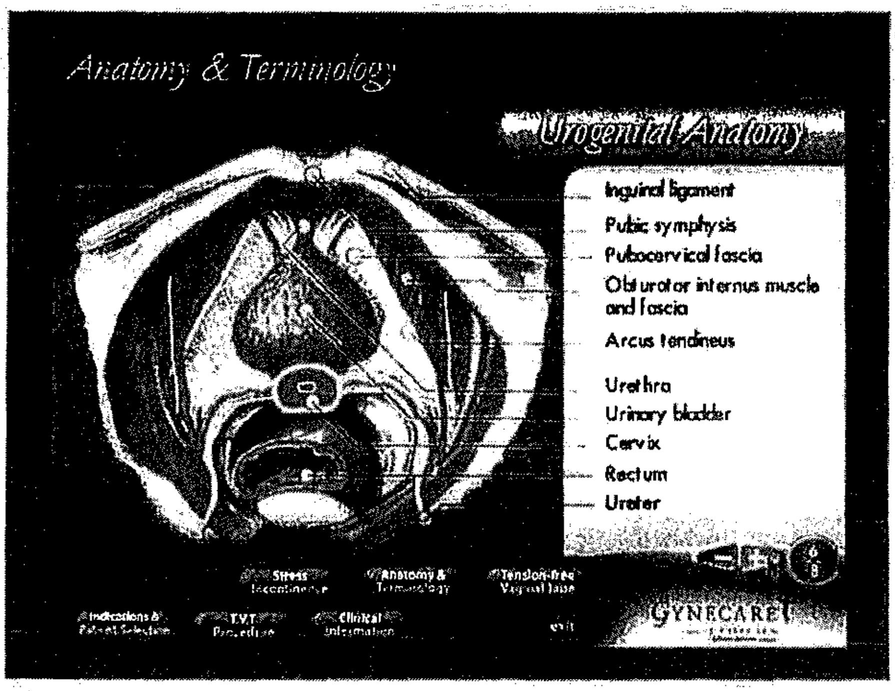
GYNECARE TVT Tension-free Support for Incontinence

Pelvic Diaphragm - Female

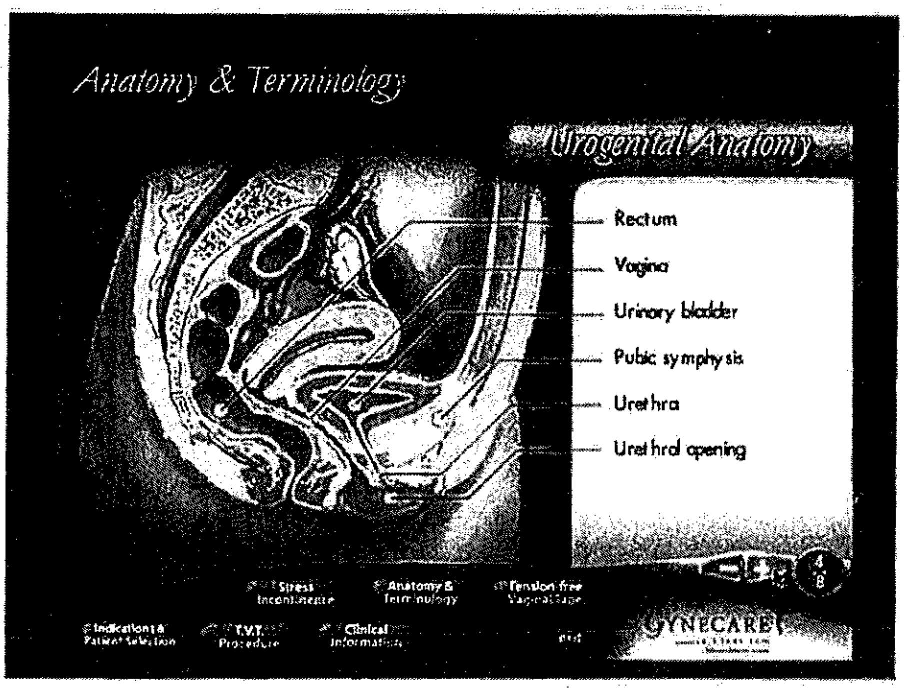
Medial View



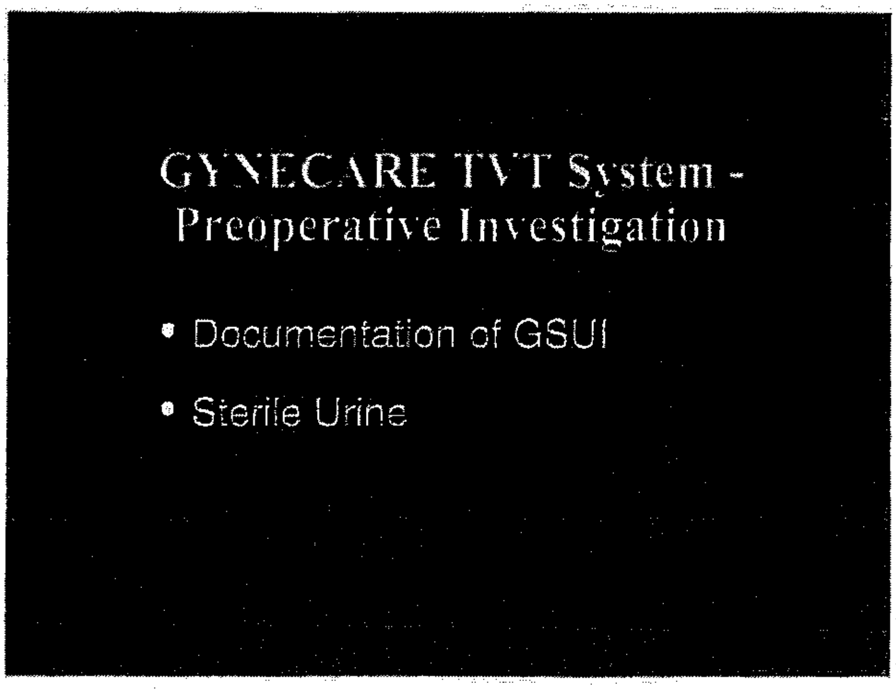
GYNECARE TVT Tension-free Support for Incontinence


Anatomy & Terminology
Urogenital Anatomy
Inguinal ligament
Pubic symphysis
Pubocervical fascia
Obturator internus muscle and fascia
Arcus tendineus
Urethra
Urinary bladder
Cervix
Rectum
Ureter
Stress
Anatomy &
Tension-free
Indications &
T.V.T
Clinical
exit
GYNECARE

GYNECARE TVT Tension-free Support for Incontinence



Anatomy & Terminology
Urogenital Anatomy
Rectum
Vagina
Urinary bladder
Pubic symphysis
Urethra
Urethral opening
Stress Incontinence
Anatomy & Terminology
Tension-free Vaginal Tape
Indications & Patient Selection
T.V.T. Procedure
Clinical Information
GYNECARE


GYNECARE TVT System - Preoperative Investigation
• Documentation of GSUI
• Sterile Urine

As with other anti-incontinence operations, the preoperative investigation should establish the diagnosis of genuine stress urinary incontinence and the absence of urinary tract infection.

GYNECARE TVT Tension-free Support for Incontinence

GYNECARE TVT tension-free support
Patient Information

- Potential risks
  - bleeding-hematoma formation
  - infection
  - perforation
    - bladder
    - bowel
  - urinary retention
  - nerve injury
  - foreign body response

Patients should be counseled about the potential risks and benefits of the procedure.

Complications are infrequent, but may include the following:

•Punctures or lacerations of vessels, nerves, bladder, or bowel may occur during needle passage. They may require surgical repair and may be serious if not recognized and managed appropriately.

•Transitory local irritation at the wound site or a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation or inflammation.

•As with all foreign bodies, PROLENE mesh may potentiate an existing infection. The plastic sheath initially covering the PROLENE mesh is designed to minimize the risk of contamination.

•Overcorrection, i.e., too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction leading to difficult voiding or the inability to void.

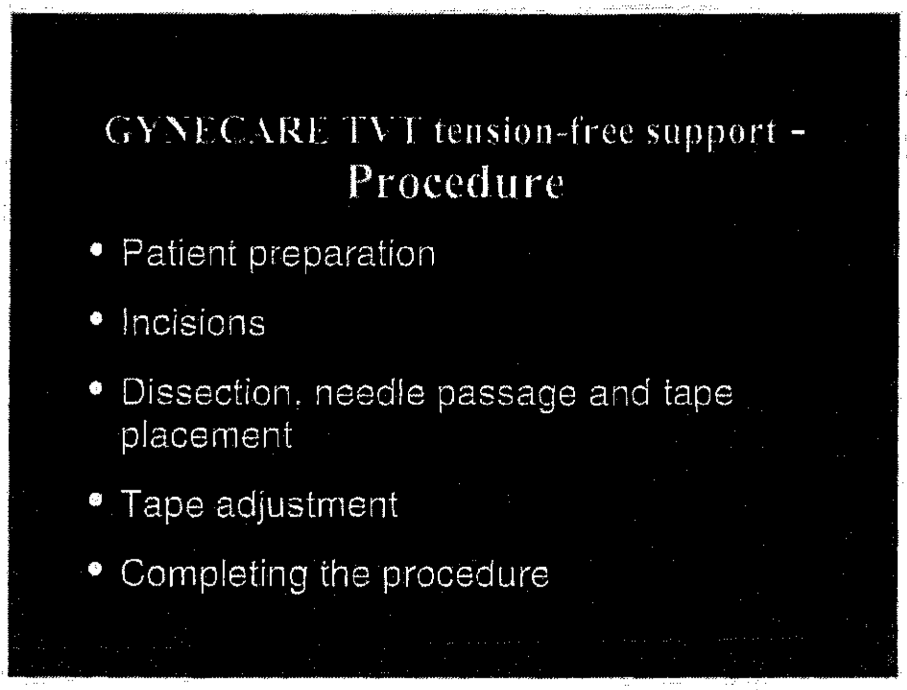
GYNECARE TVT Tension-free Support for Incontinence

GYNECARE TVT tension-free support -
Pre Op

- NPO
- Peri-operative antibiotics
- Cessation of anti-coagulants
- Postmenopausal patient should have estrogenized vaginal mucosa

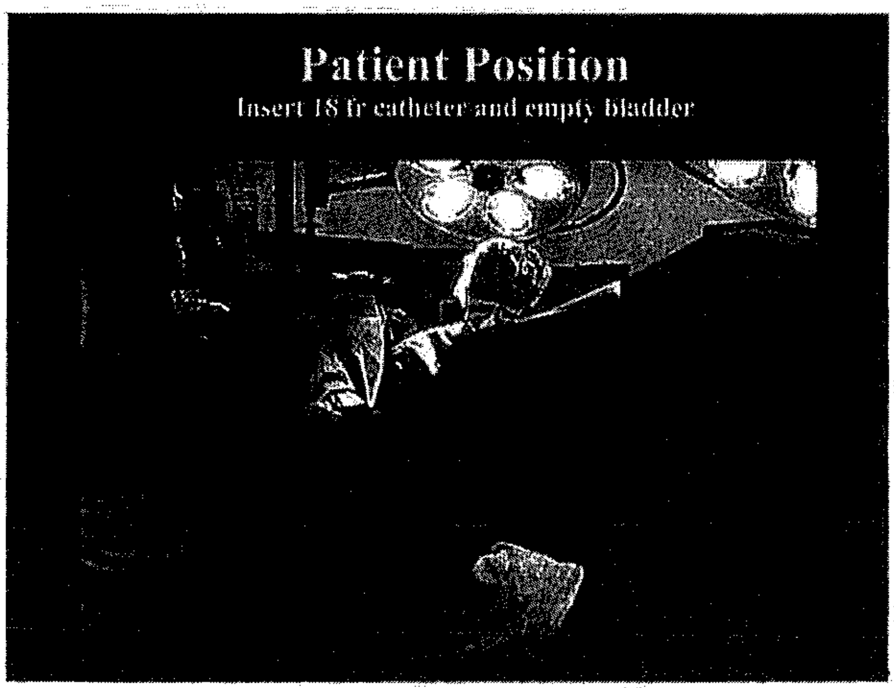
Patients should be NPO for 12 hours before the procedure. Prophylactic antibiotics that cover urinary tract pathogens are advised and aspirin and other anticoagulants shall be discontinued for an adequate period before surgery. Systemic or local estrogen should be considered.

GYNECARE TVT Tension-free Support for Incontinence


GYNECARE TVT tension-free support -
Procedure
• Patient preparation
• Incisions
• Dissection, needle passage and tape placement
• Tape adjustment
• Completing the procedure

Preparation includes positioning and anesthetizing the patient.

GYNECARE TVT Tension-free Support for Incontinence


Patient Position
Insert 18 fr catheter and empty bladder

The patient is draped and placed in dorsal lithotomy, utilizing boot-type stirrups. An 18 fr catheter is inserted and the bladder is emptied.

GYNECARE TVT Tension-free Support for Incontinence

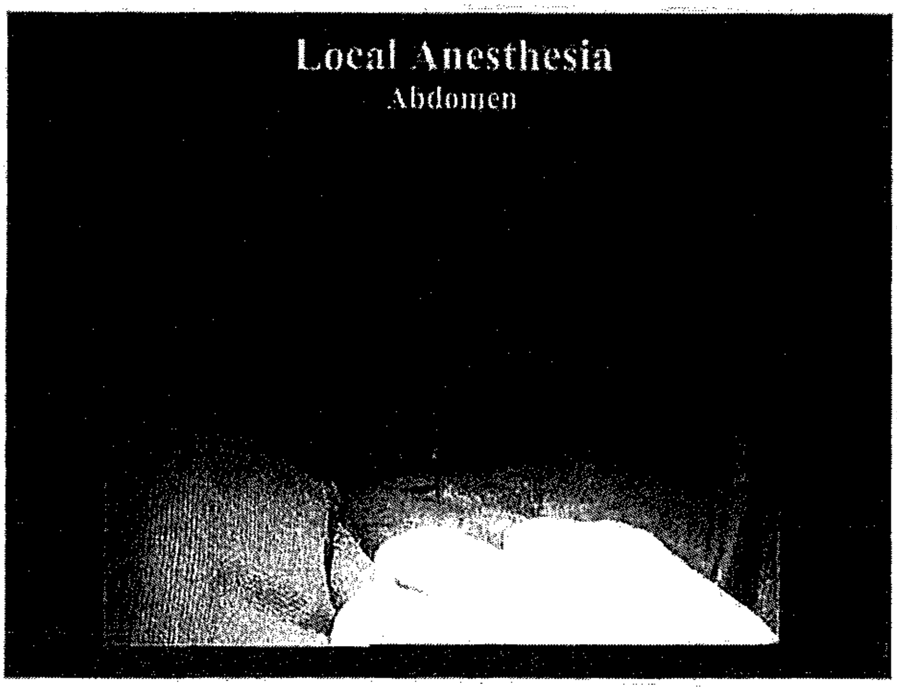
Anesthesia

- Discuss steps of procedure with anesthesiologist/anesthetist prior to case
- Local anesthesia with IV sedation recommended
- Inject local anesthetic into subcutaneous and muscle/fascia layer
- Regional or general anesthesia possible

A cough test, which will be described later, requires patient participation during the incontinence repair procedure using GYNECARE TVT tension-free support. Therefore, it is recommended that the incontinence repair procedure be preformed under local anesthesia with IV sedation. However, regional or general can be used by surgeons experienced with the procedure, provided the surgeon places the mesh loosely under the mid-urethra. Ensure proper positioning by spacing the tape with a blunt instrument.

Selection of regional anesthesia should be made with the understanding that the patient will need to cough during the procedure. It is recommended that the surgeon works closely with the anesthesiologist to choose a regional that will not relax the pelvic anatomy and will allow the patient to cough normally.

GYNECARE TVT Tension-free Support for Incontinence

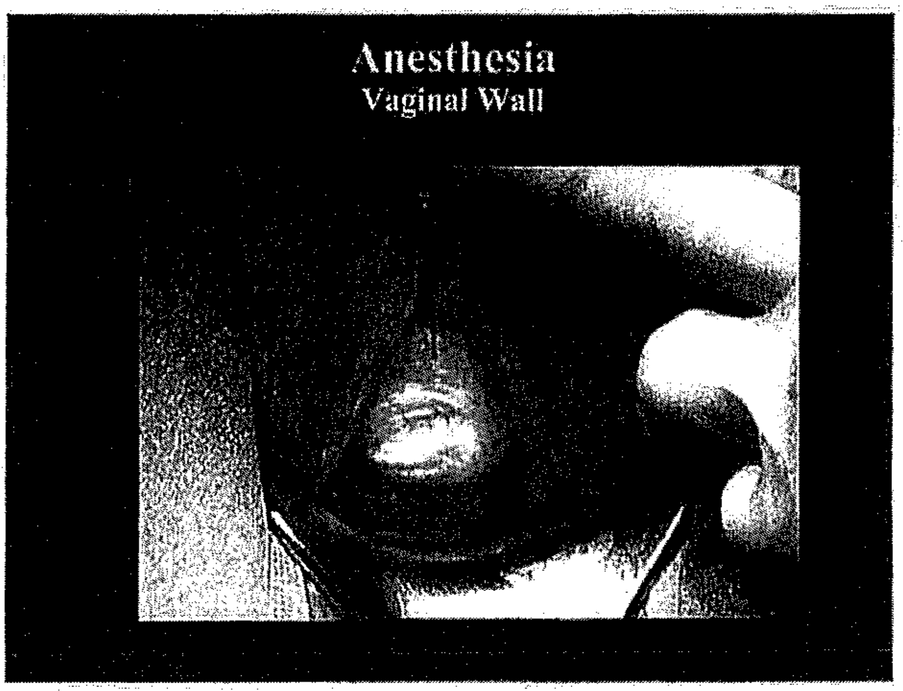


Inject local anesthesia in the skin just above the symphysis on both sides of the midline.

Continue on each side in the abdominal wall, into the muscles and fascia. Inject anesthesia behind the pubic symphysis into the retropubic space.

This is one technique and other techniques may vary.

GYNECARE TVT Tension-free Support for Incontinence



Insert the speculum.

Inject local anesthesia sub-urethrally, starting approximately 1.0 cm from the external urethra meatus.

Inject local on each side of the urethra into the retropubic space.

Allow 3-4 minutes for the anesthesia to take affect.

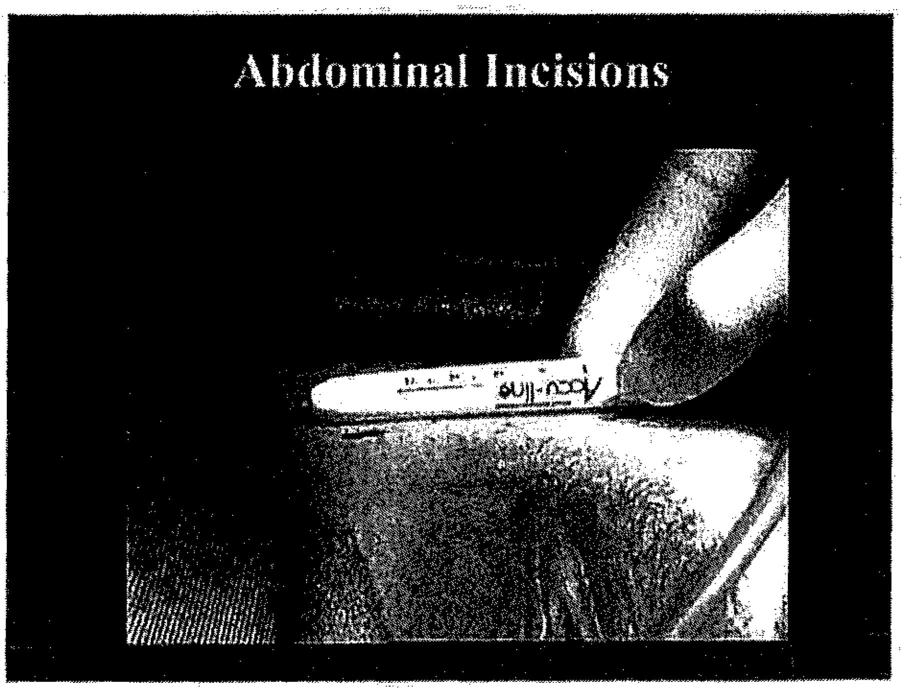
GYNECARE TVT Tension-free Support for Incontinence

Incisions

-
  - 1.5 cm (vertical and suburethral)
  - 1.0 cm from external urethral meatus
-
  - 1 incision each side of midline
  - 0.5 cm - 1.0 cm
  - just above symphysis
  - not more than 4 - 5 cm apart

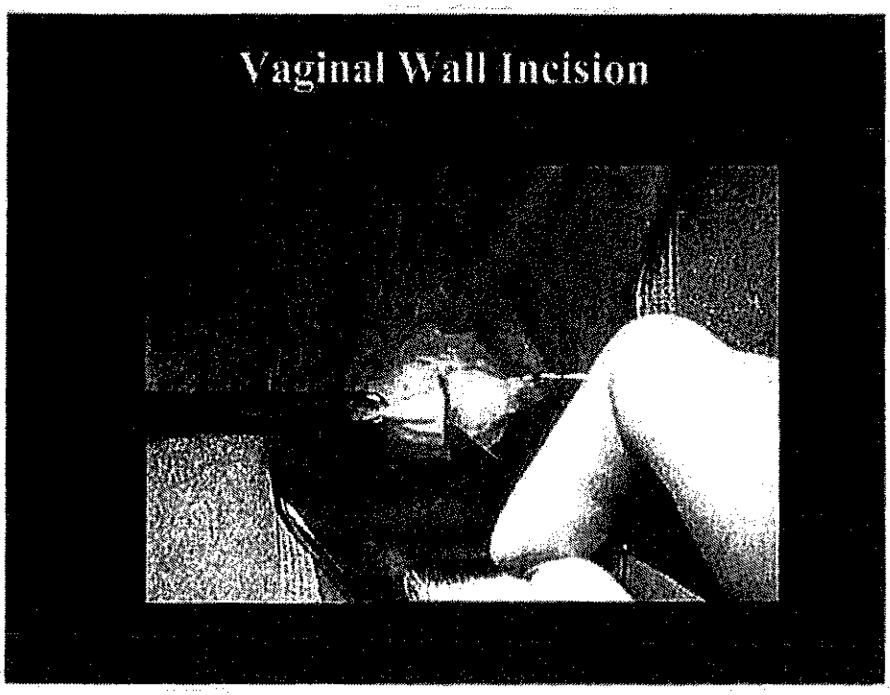
The surgeon then proceeds with the suprapubic and vaginal incisions.

GYNECARE TVT Tension-free Support for Incontinence



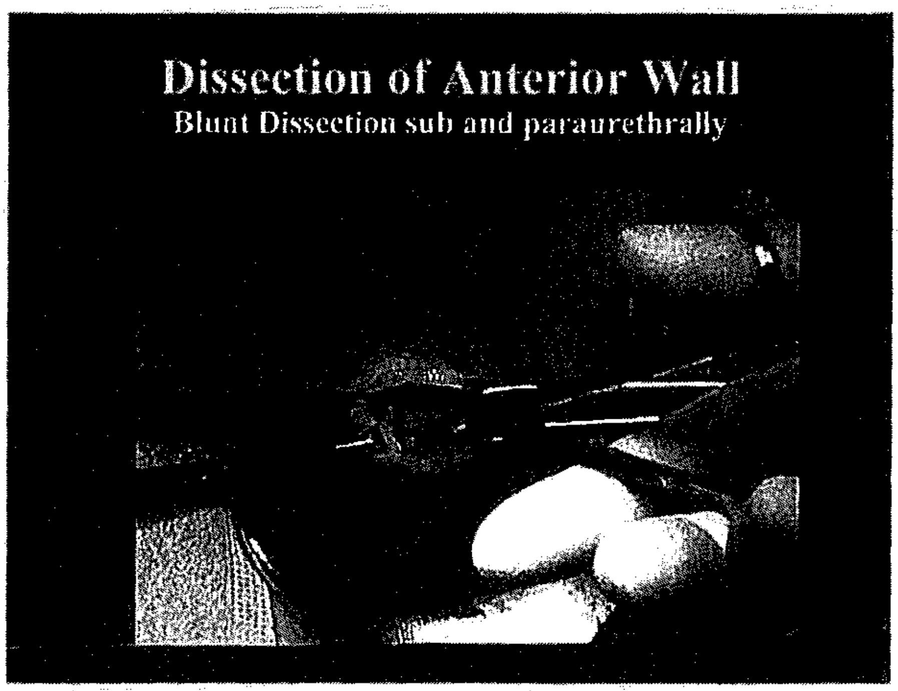
Two small incisions of .5 cm - 1.0 cm are made just above the pubic symphysis. These incisions are made about 2 cm on each side of the midline. The maximum distance between the incisions should be 4-5 cm. These are skin incisions only, no dissection is necessary.

GYNECARE TVT Tension-free Support for Incontinence



The anterior vaginal wall overlying the mid to distal urethra is elevated with Allis clamps and incised vertically in the midline. The incision should begin approximately 1.0 cm from the external urethra meatus and extend for 1.5 cm to accommodate the width of the TVT tape.

GYNECARE TVT Tension-free Support for Incontinence

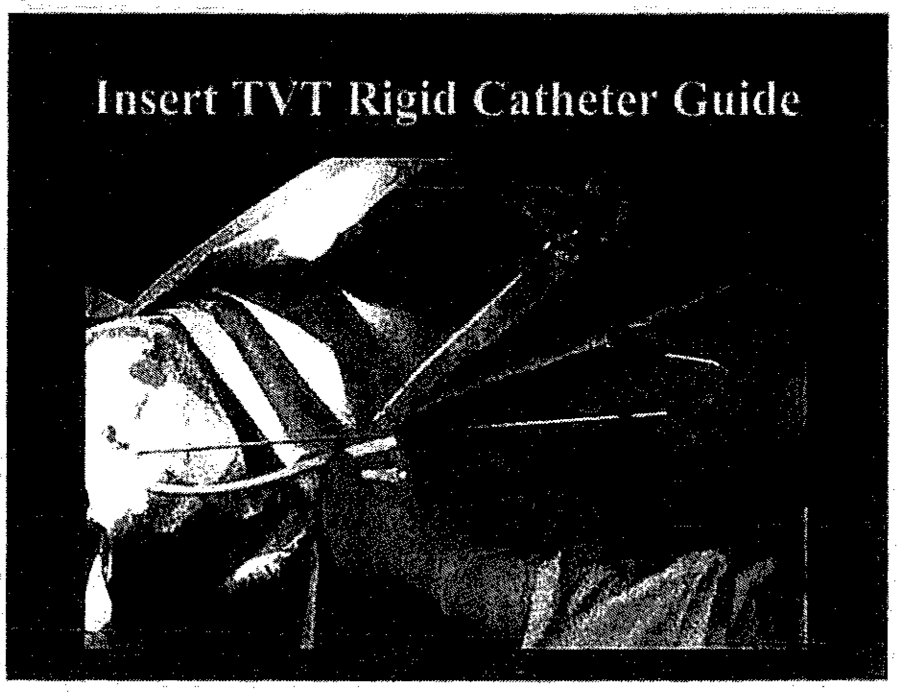

Dissection of Anterior Wall
Blunt Dissection sub and paraurethrally

The incontinence repair procedure using GYNECARE TVT tension-free support proceeds with dissection, needle passage and placement of the tape.

Lateral dissection should extend only 1.5cm.

Metzenbaum scissors are used to dissect the vaginal incision sub and paraurethrally. Care should be taken not to puncture the pubocervical fascia. The purpose of this dissection is to make a space lateral to the urethra which is the starting position for the TVT needle. The dissection through the pubocervical fascia, into the retropubic space and up to the abdomen is completed with the TVT needle.

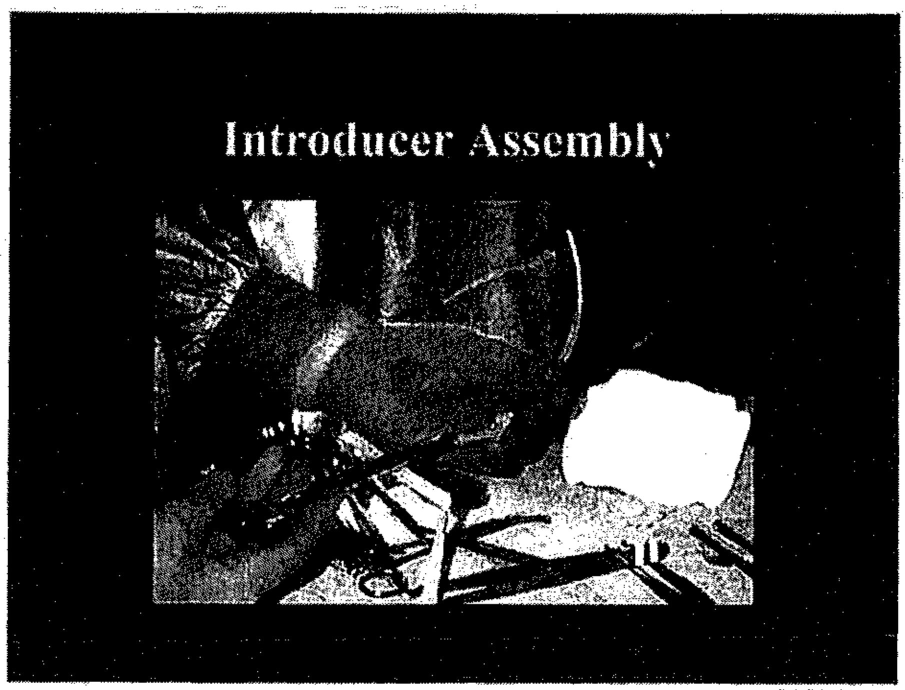
After dissecting paraurethrally additional local anesthesia should be applied transvaginally, administered to the underside of the pubic symphysis (approx 20 cc on each side).



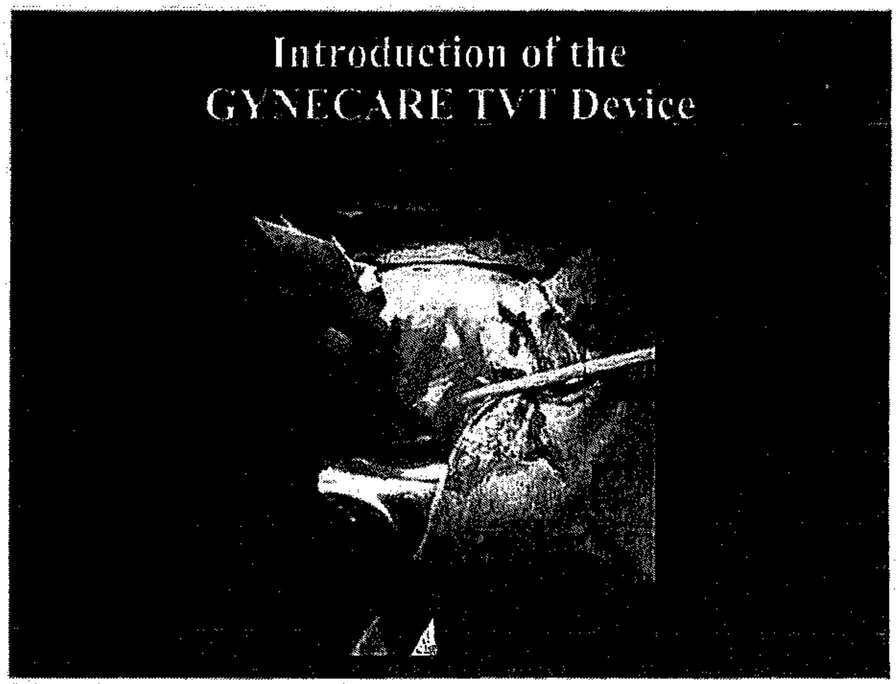
Uncap Foley and drain bladder.

Insert the TVT Rigid Catheter Guide into the 18 Fr Foley catheter. This is completed while the catheter is out of the bladder to ensure that the catheter guide is inserted properly in the catheter. The purpose of the TVT catheter guide is to help identify the urethra and most importantly to move the bladder neck from the path of the needle passage. After the guide is placed in the catheter, the handle is gently pushed inward and lateral to the side of needle passage. Moving the handle of the guide to the patients side where the needle will pass will move the bladder away from the path of the needle.

GYNECARE TVT Tension-free Support for Incontinence


Introducer Assembly

GYNECARE TVT Tension-free Support for Incontinence



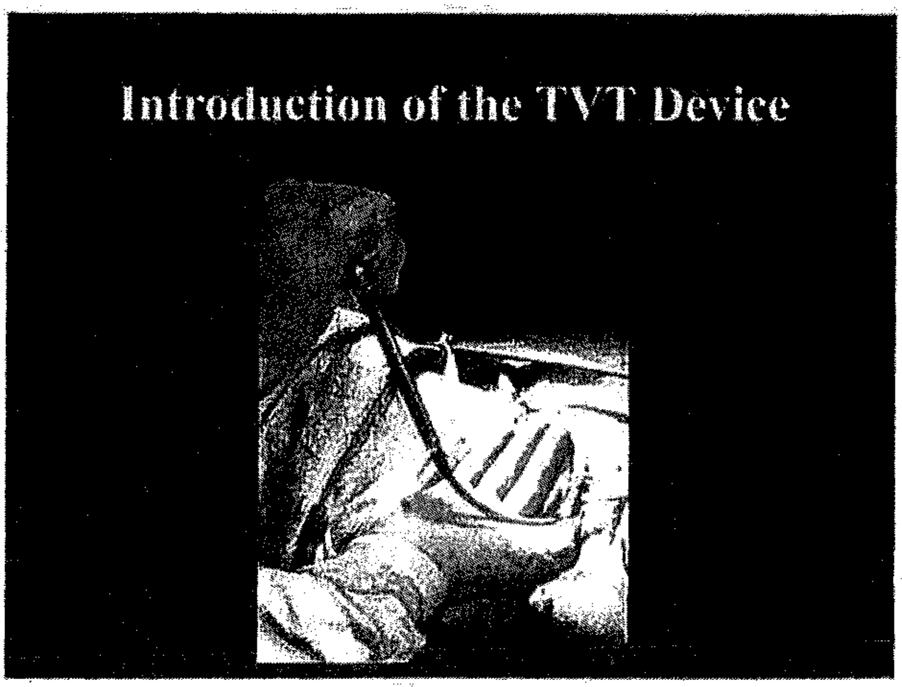
Remove the Speculum.

Assemble the needle and introducer. Place the needle tip in the starting position within the paraurethral incision.

With one hand take a gentle grip on the introducer. Position the needle tip through the vaginal incision lateral to the urethra. Your other hand should be placed where your index or middle finger can be placed on the pelvic rim under the vaginal wall. The curve of the TVT needle should rest in the palm of this hand. As the needle is passed into the retropubic space you should feel the needle pass behind the pubic bone. Correct positioning is as follows: pass the needle tip lateral to the urethra and horizontal, aiming towards the ipsilateral shoulder while perforating the pubocervical fascia.

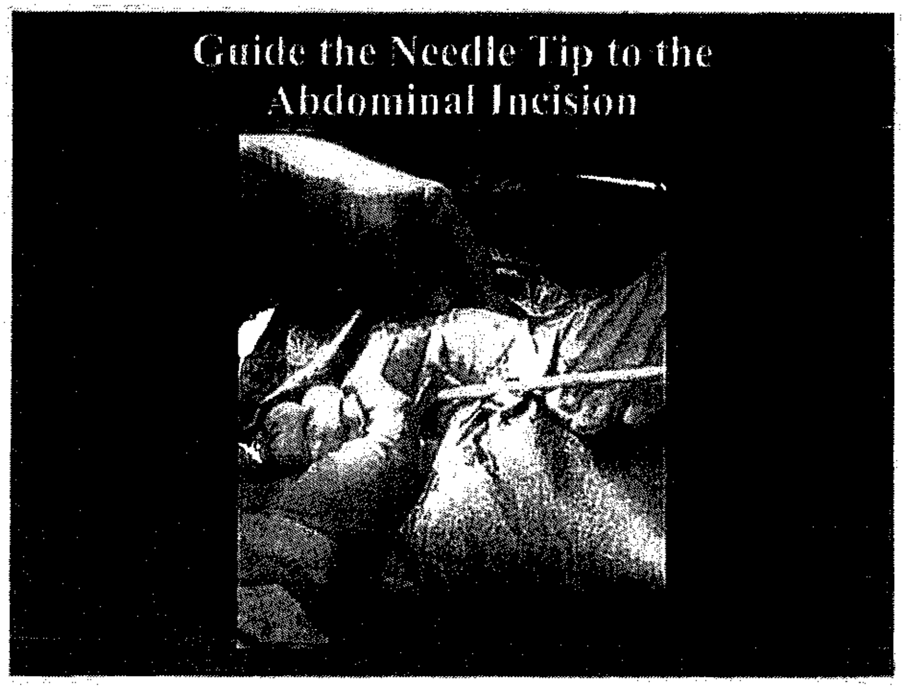
At this point, preceptor should show proper device handling and correct hand positioning as indicated above.

GYNECARE TVT Tension-free Support for Incontinence


Introduction of the TVT Device

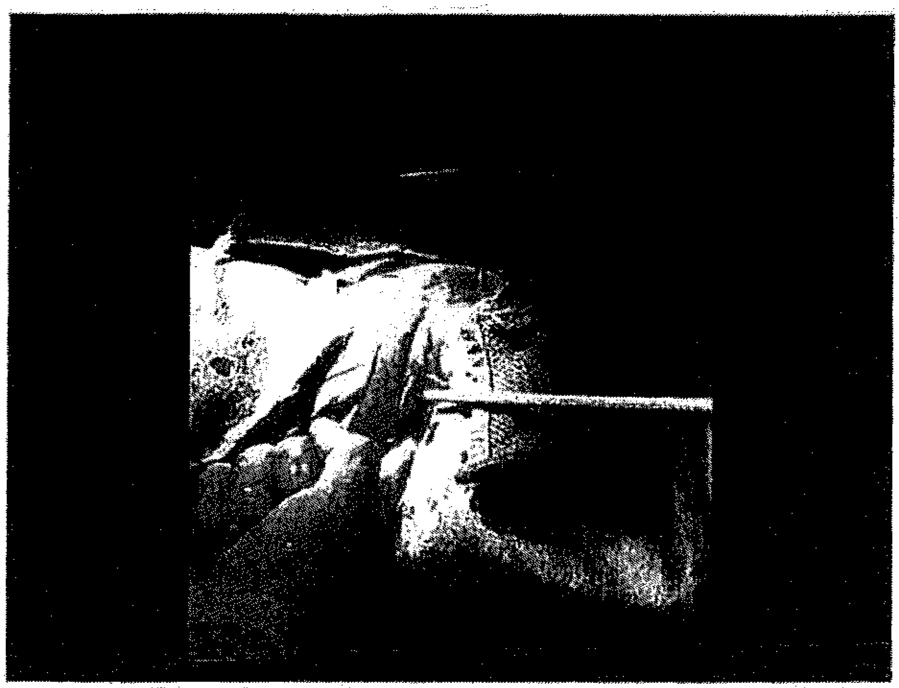
Confirm proper alignment of needle using ipsilateral axillary landmark.

GYNECARE TVT Tension-free Support for Incontinence



- Care should be taken to slide the tip of the needle along the inner edge of the inferior pubic ramus.
- The needle should be advanced slowly until resistance is felt. If the surgeon advances the needle more than 2 cm without penetrating the pubocervical fascia, he or she should pull back and reorient the needle. This will occur if the needle is angled too far laterally such that it is penetrating the obturator internus muscle.

GYNECARE TVT Tension-free Support for Incontinence



- Immediately upon piercing endopelvic fascia, direct tip of needle ventrally by moving handle downward
- Aim the tip of needle toward the abdominal midline and upward to abdominal incision, keeping the angle of the instrument pointed toward the ipsilateral shoulder.
- Keep the needle in close contact with the back of the pubic bone.

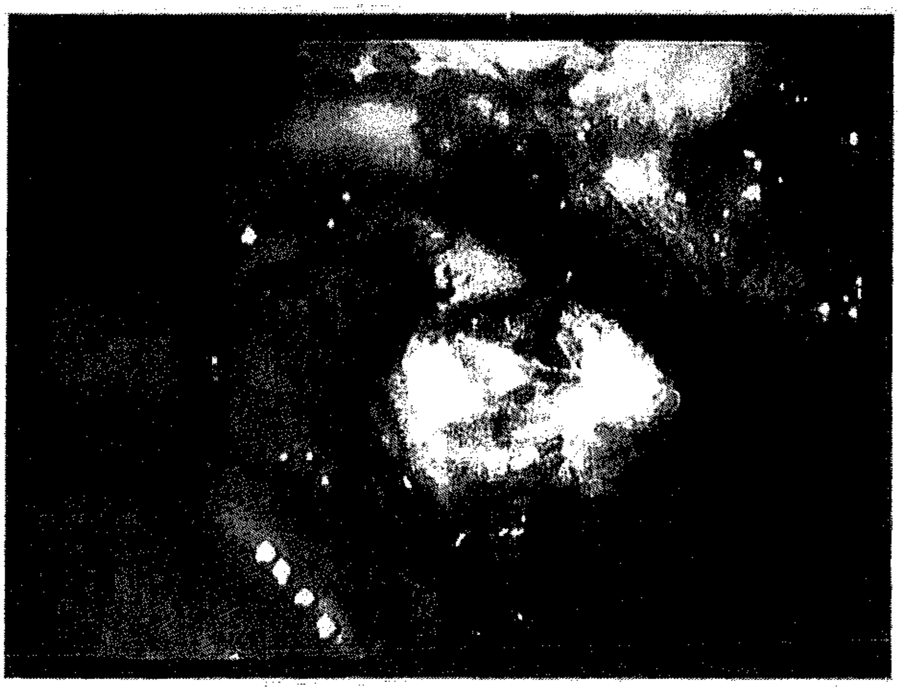
After penetration of the abdominal fascia, one hand can be used to guide the needle tip through the suparpubic incision. After the needle tip has cleared the surface of the abdomen, release the needle from the introducer.

GYNECARE TVT Tension-free Support for Incontinence

Laparoscopic View
GYNECARE TVT Needle
Passage

ETH.MESH.05795464

GYNECARE TVT Tension-free Support for Incontinence

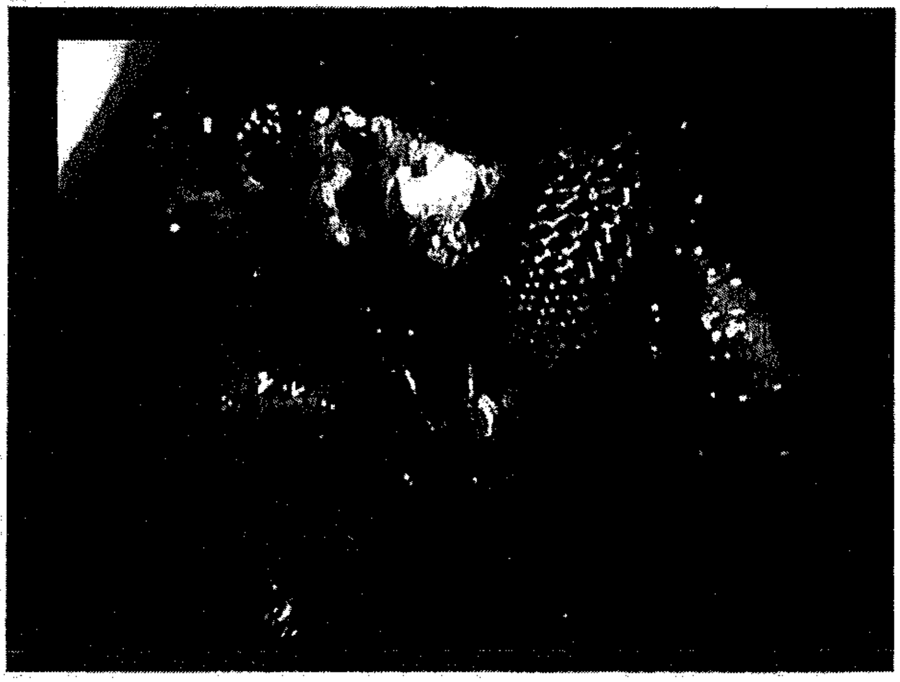


This is a photo of the needle passing through the pubocervical fascia approx. 2 cm lateral to the mid-urethral level on the patient's right side.

GYNECARE TVT Tension-free Support for Incontinence

This is a photo of the needle passing through the pubocervical fascia approx. 2 cm lateral to the mid-urethral level and passing through the anterior abdominal wall toward the right suprapubic incision.

GYNECARE TVT Tension-free Support for Incontinence



Here the PROLENE mesh with plastic sheath has been pulled up through the abdominal incision.

Cystoscopy

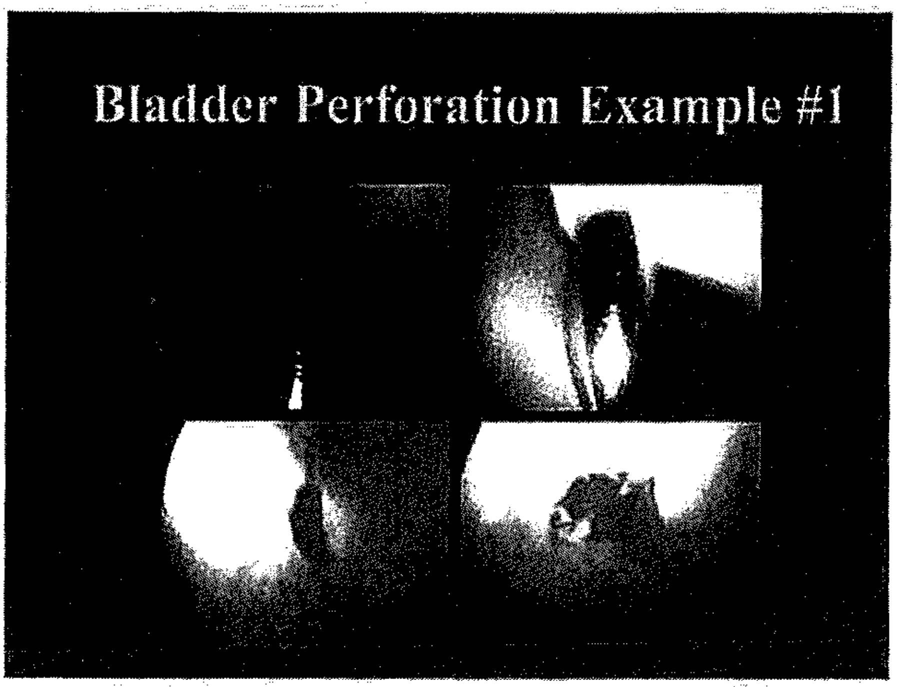
- After each passage of the needle, cystoscopy should be completed to verify bladder integrity
- Cystoscopy should be done with the bladder filled with at least 250cc of sterile water

Urethrocystoscopy is performed after each passage of the introducer needle through the vagina and abdominal wall to verify that the lower urinary tract has not been injured.

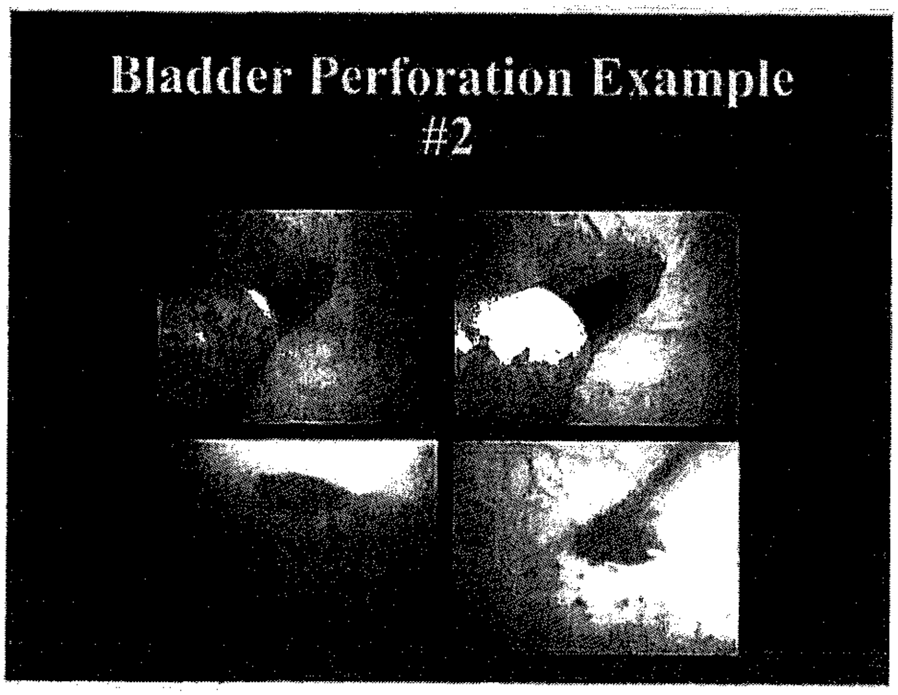
The cystoscopy should be preformed with the **needle in situ**, with complete examination of the bladder and urethra. The purpose of cystoscopy at this point in the procedure is to identify bladder perforation. Also, the needle can be removed and re-introduced more laterally. If the needle is passed completely through the abdominal incision, then the the tape would have to be cut in order to remove it from the bladder. Destruction of the mesh would necessitate opening a new device to complete the procedure.

After bladder integrity has been confirmed, the needles should be pulled through the retropubic space and placed on the abdomen.

GYNECARE TVT Tension-free Support for Incontinence


Bladder Perforation Example #1

GYNECARE TVT Tension-free Support for Incontinence


Bladder Perforation Example
#2

Second Passage of the GYNECARE TVT Device

- Re-insert the catheter and drain the bladder
- Repeat the procedure on the opposite side in the same manner
- Ensure that the mesh does not twist
- Fill the bladder and perform cystoscopy after the second pass of the TVT needle
- Pull TVT needle completely through the abdominal incision only after bladder integrity has been confirmed.

For the second pass of the needle, reinsert the Foley catheter into the bladder and allow the saline to drain. Insert the catheter guide and again move the handle to the same side the needle will pass. As the needle tip is placed in starting position ensure that the mesh is not twisted.

Perform the second needle passage in the same manner as the first.

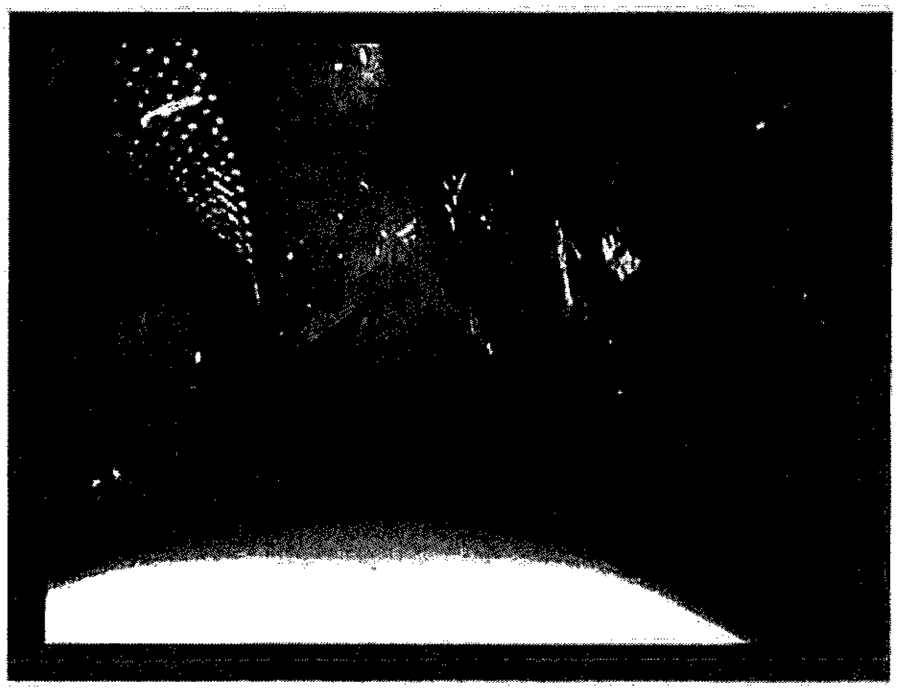
Conduct a second cystoscopy.

After bladder integrity is confirmed pull the second needle through to the abdomen.

GYNECARE TVT Tension-free Support for Incontinence

This is a photo of the needle going through the pubocervical fascia approx. 2 cm lateral to the mid-urethral level on the patient's left side.

GYNECARE TVT Tension-free Support for Incontinence



Both needles have been passed and the mesh tape with plastic sheathe is now in place.

Mesh Adjustment

- Place closed scissors, a hemostat, or a Hegar dilator between the tape and the urethra
- Pull the abdominal ends of the tape until there is contact between the tape and the instrument, while ensuring that the mesh is not twisted
- Separate the needles from the tape by cutting the plastic sheath and tape directly below the needles
- Do not remove the plastic sheath

After placement of the mesh and prior to removal of the protective sheath, position the tape while the patient coughs.

Before starting the cough test, place scissors or a hemostat between the tape and urethra. Pull the abdominal end of the tape until there is slight contact between the tape and the instrument.

Cut the needles from the tape.

Do not remove the plastic sheath.

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GYNECARE TVT Tension-free Support for Incontinence

Cough Test

- The bladder should still be filled from the second cystoscopy.
- Remove all instruments from urethra and vagina and simulate a closed vaginal wall by reapproximating vaginal wall gently using small forceps.
- Ask patient to cough:
  - If a vigorous cough cannot be solicited, consider allowing sedative to reverse, placing 50-100ml of additional saline in bladder, and/or repositioning the patient to reverse Trendelenburg.
  - On vigorous coughing:
  - Patient should leak urine on first cough. If not, loosen tape by placing instrument between tape and urethra
  - Pull up on mesh (with instrument in place) and perform cough test again, repeating until just a few drops of urine are present

The cough test should be conducted with a full bladder.

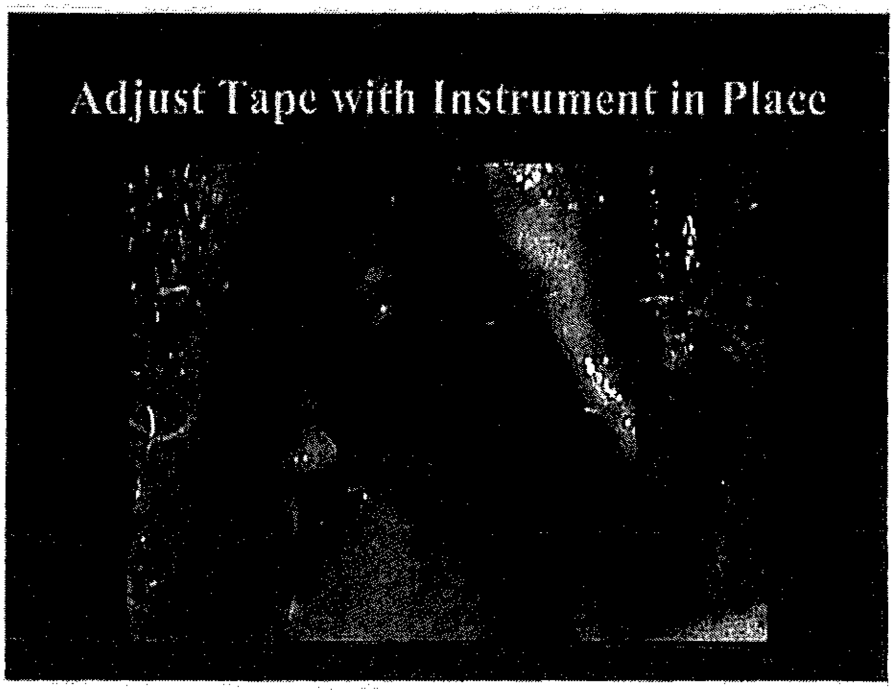
The test should be preformed after removing all instruments. There should be no artificial pressure on the vaginal walls.

During the cough test cooperation with the anesthesiologist is recommended. At this point in the procedure the patient should be aware and able to generate a normal cough.

After the first cough if the patient leaks, reinsert the instrument between the urethra and mesh and pull upwards slightly from the abdominal ends. Ask patient to cough again.

The tape should be positioned so that during the cough test only one or two drops of urine leak. The purpose of this is to ensure that the tape is not overly tensioned under the urethra.

GYNECARE TVT Tension-free Support for Incontinence


Adjust Tape with Instrument in Place

Completing the Procedure

- Remove plastic sheath being careful not to alter position of mesh
- Cut PROLENE Mesh just below the skin - Note: do not suture or anchor the abdominal ends of the mesh
- Close skin and vaginal epithelium
- Empty bladder
- Remove catheter
- Assess for urethral compression by passing Hegar dilator through urethra

Identify the plastic sheath at the abdominal ends of the mesh and grasp it with forceps.

Place an instrument, scissors or forceps, between the urethra and the mesh. Hold the mesh in place and remove the plastic sheath. The sheath has preformed its two major tasks. It has protected the tape during insertion and it has provided a smooth transition for the mesh through the tissues.

The mesh is now in place, without tension, underneath the mid-urethra.

Cut the abdominal ends of the mesh just below the surface of the skin.

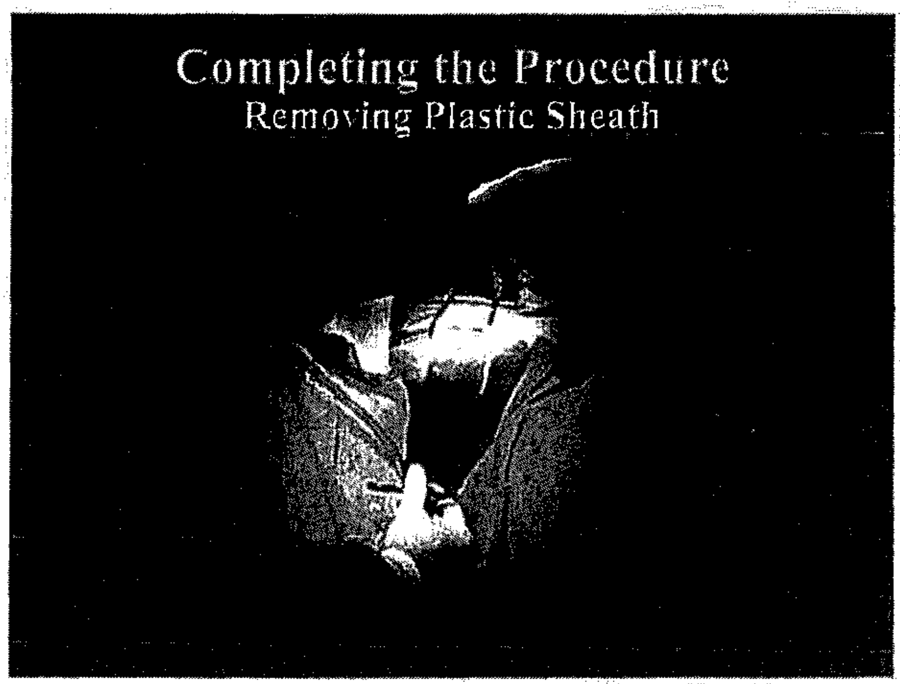
DO NOT SUTURE OR ANCHOR THE ABDOMINAL ENDS OF THE MESH. The friction from the opposing tissues to the mesh secures the mesh in place.

Close the incisions in a normal manner.

Complete testing with a Hegar dilator number 7-8. When inserted through the urethra there should be no resistance, i.e., the mesh should not be noticed, Also, check that the proximal urethra is not in a fixed position. The bladder neck should be mobile.

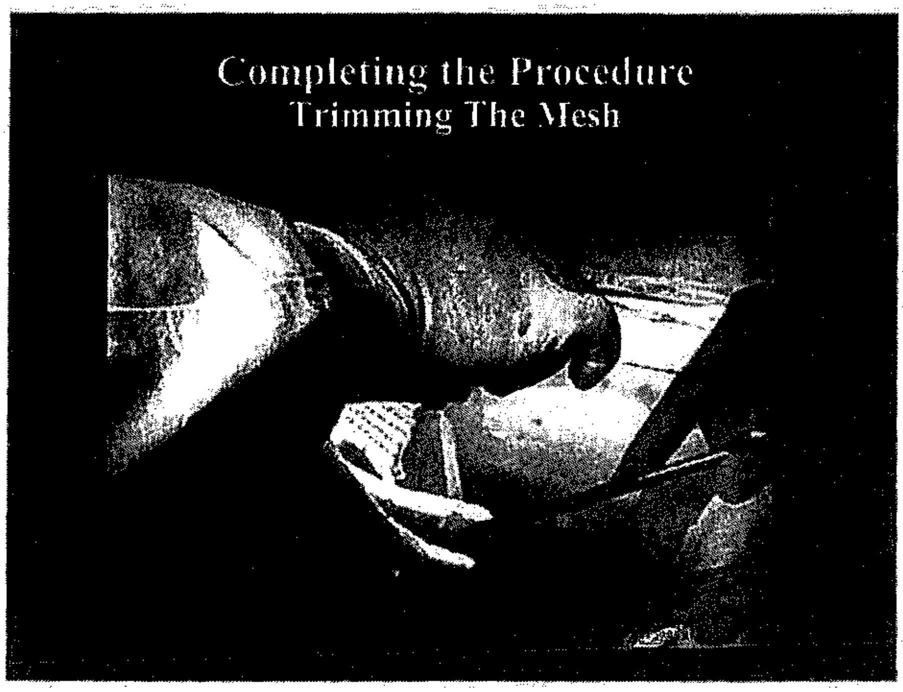
Empty bladder and remove catheter.

GYNECARE TVT Tension-free Support for Incontinence


Completing the Procedure
Removing Plastic Sheath

Identify the plastic sheath at the abdominal ends of the mesh and grasp it with forceps.

GYNECARE TVT Tension-free Support for Incontinence

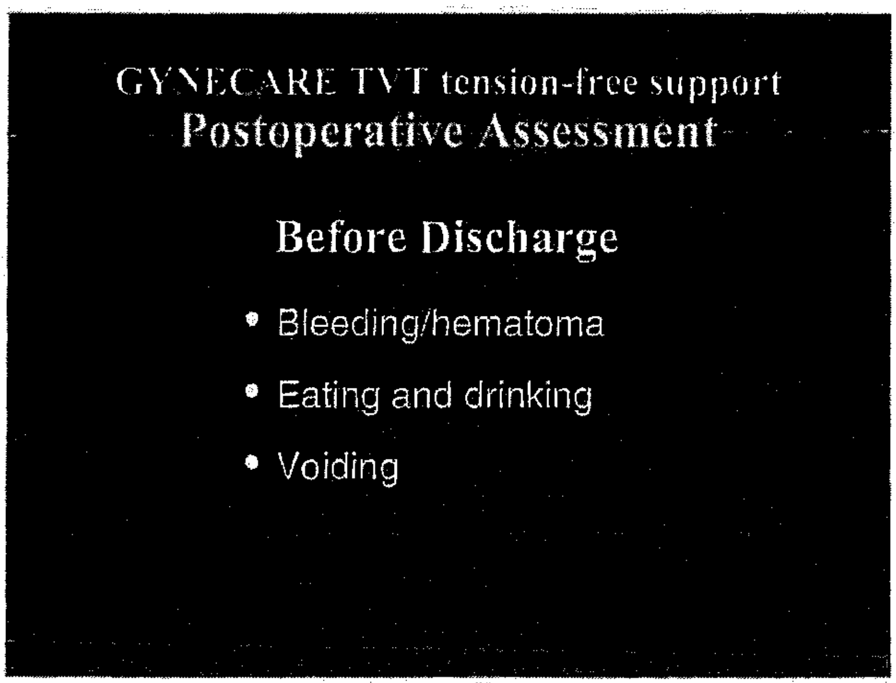

Completing the Procedure
Trimming The Mesh

Cut the abdominal ends of the mesh just below the surface of the skin.

DO NOT SUTURE OR ANCHOR THE ABDOMINAL ENDS OF THE MESH. The friction from the opposing tissues to the mesh secures the mesh in place.

Close the incision in a normal manner.

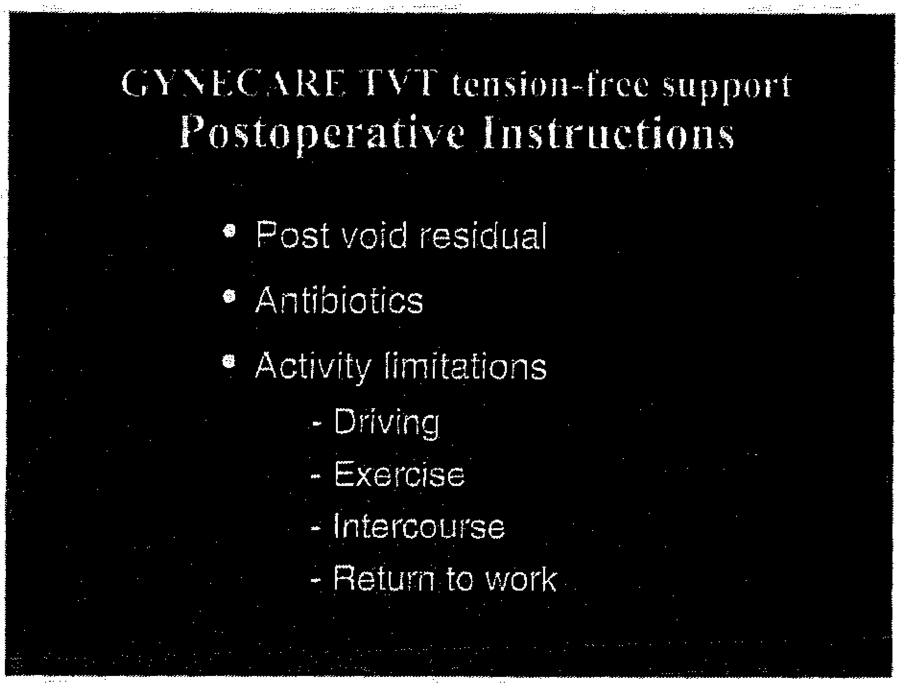
GYNECARE TVT Tension-free Support for Incontinence


GYNECARE TVT tension-free support
Postoperative Assessment
Before Discharge
• Bleeding/hematoma
• Eating and drinking
• Voiding

Postoperatively, the patient is observed for signs of bleeding. There are no restrictions on eating and drinking, and the patient is encouraged to void normally.

At this point please reference the Postoperative Care page in the Preceptee Binder.

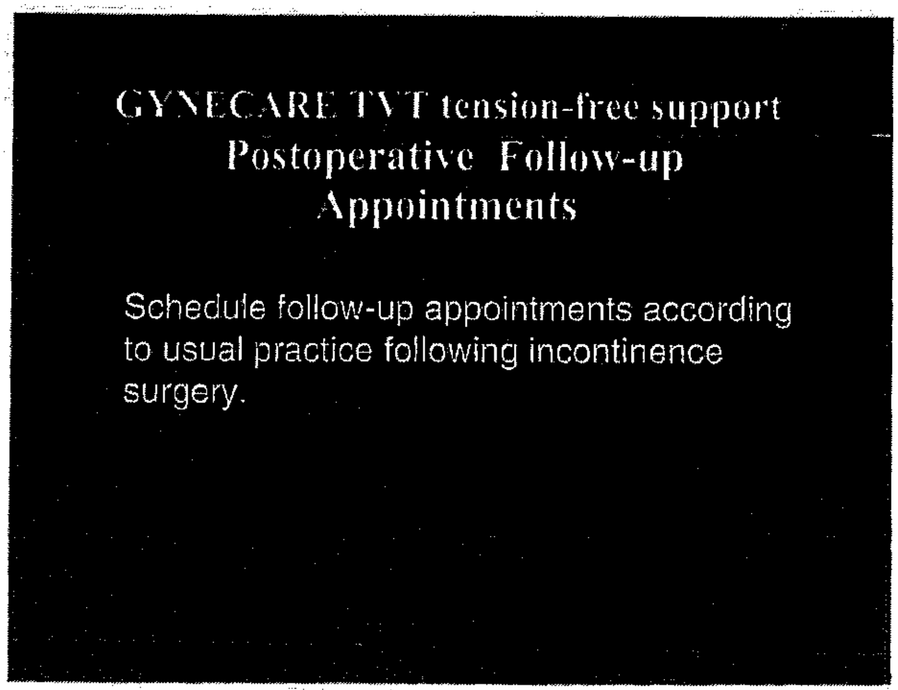
GYNECARE TVT Tension-free Support for Incontinence


GYNECARE TVT tension-free support
Postoperative Instructions
• Post void residual
• Antibiotics
• Activity limitations
- Driving
- Exercise
- Intercourse
- Return to work

Residual urine is measured to rule out retention. Prophylactic antibiotics may be prescribed according to local practice.

Post-operatively instruct the patient to restrict her normal activity for one or two weeks depending on usual level of activity. Advise her to refrain from heavy exercise (i.e., cycling, jogging, and lifting) for at least four to six weeks, and to refrain from intercourse according to usual practice following vaginal surgery (at least 1 month).

GYNECARE TVT Tension-free Support for Incontinence


GYNECARE TVT tension-free support
Postoperative Follow-up
Appointments
Schedule follow-up appointments according to usual practice following incontinence surgery.

After an initial follow-up at 3 weeks, patients are seen at 6 months and annually.

GYNECARE TVT Tension-free Support for Incontinence

GYNECARE TVT Tension-free Support for Incontinence
Minimizing Risks & Recommendations for Management

Please review the Warnings and Precautions section of the Preceptee binder at this point. The adverse reactions should also be reviewed.

GYNECARE TVT Tension-free Support for Incontinence

The following discussion of complications is from the surgeon's resource monograph: Expert opinion on the use of GYNECARE TVT Tension-free Support for Incontinence.

GYNECARE and ETHICON, INC. do not take a position as to how any individual patient should be treated. The medical opinions expressed are those of the physicians contributing to the monograph (Carl Klutke, M.D., Eric Kuhn, M.D., and Vincent Lucente, M.D., June 2000 Summit Meeting). It is the responsibility of the patient's surgeon to make appropriate decisions based on individual patient circumstances.

GYNECARE TVT Tension-free Support for Incontinence

Complication: Vascular Injury

PREVENTION:

- Avoid hip flexion greater than 60° and consider using low knee support stirrups
- Direct needle along cephalad surface of pubic bone
- Stay close to the mid-line and avoid lateral insertion of the needle
- Ensure abdominal incisions are medial to the pubic tubercle

INTERVENTION:

- For minor/venous bleeding consider electrocautery or direct pressure using finger or pack
- For major/arterial hemorrhage:
  - initiate patient support
  - consider open intervention
  - consider radiographic embolization

GYNECARE TVT Tension-free Support for Incontinence

Complication: Urethral Erosion

PREVENTION:

- Avoid excessive dissection
- Avoid placement of device under tension

INTERVENTION:

- Consider local excision of mesh, layered closure of urethra and an indwelling urethral catheter for several days

GYNECARE TVT Tension-free Support for Incontinence

Complication: Vaginal Extrusion of Mesh*

PREVENTION:

- Ensure vaginal closure (inspect for button-holes)
- Counsel patient to avoid intercourse until healed (4-6 weeks)

INTERVENTION:

- Consider treating post-operative infection with antibiotics and estrogen
- Consider trimming the mesh and restoring the vaginal mucosa

*The risk of vaginal mesh extrusion may be increased in women with post-operative infection, previous vaginal surgery, vaginal atrophy, or vaginal injury.

GYNECARE TVT Tension-free Support for Incontinence

Complication: Bowel Perforation

PREVENTION:

- Direct needle along cephalad surface of pubic bone
- Consider pre-operative imaging for patients with previous surgery (review operative notes)
- Consider placing patient in Trendelenburg position if concurrent laparoscopy is being performed

INTERVENTION:

- Aggressively evaluate signs or symptoms suggestive of peritonitis
  - imaging
  - open exploration

GYNECARE TVT Tension-free Support for Incontinence

Complication: Urinary Retention

PREVENTION:

- Pre-operatively consider urodynamic studies to rule out voiding dysfunction
- Intra-operatively avoid placement of device under tension and perform cough test

INTERVENTION:

- If patient is unable to void immediately post-operatively, rule out hematoma and discharge patient with indwelling catheter for 24-72 hours
- If patient is still unable to void after 72 hours, consider reopening the site under local anesthesia, placing a right-angle forceps under the mesh, and pulling down slightly on the mesh approx 5-10 mm.
- If this procedure is not performed within the first 5-10 days (prior to tissue in-growth), consider cutting the mesh under local anesthesia in the midline after 4 weeks of catheterization. Tissue in-growth will maintain continence in approx 70% of patients.

Dr. Carl Klutke presented data at the 2001 AUA that showed a retention rate of 2.8% (17 patients). Of these 17 patients who were treated by cutting the mesh in the midline at various times after surgery, 16 maintained continence and voided normally.

GYNECARE TVT Tension-free Support for Incontinence

Complication: De-Novo Urgency

PREVENTION:

- Consider pre-operative urodynamic studies to rule out voiding dysfunction
- Avoid placement of device under tension
- Perform cough test

INTERVENTION:

- If persists, consider behavioral therapy and/or an anticholinergic medication
- Consider releasing mesh under local anesthesia

GYNECARE TVT Tension-free Support for Incontinence

Complication: Bladder Perforation

PREVENTION:

- Inject local anesthetic for retropubic hydrodissection
- Ensure that the bladder is empty during needle passage
- Deviate the urethra/bladder neck
- Ensure the needle is passed along the cephalad surface of the pubic bone
- Perform cystoscopy of the bladder and proximal urethra after each pass of the needle

INTERVENTION:

- If the bladder has been entered, remove and reinsert needle
- Insert indwelling catheter for 1-2 days
- If repeated penetration occurs, consider conversion to open procedure
- Consider antibiotics for 5-7 days

GYNECARE TVT Tension-free Support for Incontinence

Complication: Vaginal Perforation

INTERVENTION:

- Remove needle
- Repair vaginal wall
- Develop slightly deeper submucosal tract

GYNECARE TVT Tension-free Support for Incontinence

Complication: Urethral Injury

- Intervention:
  - Do not place the PROLENE mesh
  - Close urethral defect primarily
  - Close vagina separately
  - Insert indwelling catheter for 7-10 days

Complication: Vaginal Bleeding / Retropubic Hematoma

PREVENTION:

- Stay close to the midline and avoid lateral insertion of the needle
- Avoid hip flexion > 60°

INTERVENTION:

- Insert vaginal pack
- Consider ultrasound to facilitate diagnosis
- Consider percutaneous drainage if symptomatic (i.e., fever, pain)

GYNECARE TVT Tension-free Support for Incontinence

Complication: Wound Infection

PREVENTION:

- Employ aseptic technique
- Consider peri-operative antibiotics
- Strive for meticulous hemostasis
-

INTERVENTION

- Consider treatment with antibiotics

GYNECARE TVT Tension-free Support for Incontinence

Complication: Urinary Tract Infection

PREVENTION:

- Consider peri-operative antibiotics
-

INTERVENTION:

- Consider antibiotics for 5 days according to culture and sensitivity
- If recurrent, consider cystoscopy to rule out foreign body

GYNECARE TVT Tension-free Support for Incontinence

GYNECARE TVT Tension-free Support for Incontinence: Statement Regarding Complications

Most Serious Reported Complications (based on over 150,000 patients treated world-wide)*

Complication	US	Ex-US	Total
Vascular Injury	2	22	24
Vaginal Mesh Exposure	10	2	12
Urethral Erosion	5	0	5
Bowel Perforation	3	5	8
Nerve Injury	1	0	1

As of May 1, 2001, 4 deaths had been reported to us on a world-wide basis out of over 150,000 cases. Two were associated with undiagnosed bowel perforations. One was associated with a woman who had a bleeding disorder who died from uncontrolled post-operative bleeding in the retropubic space. The fourth was the result of a myocardial infarction nine days after the procedure, in a woman who had a vascular injury at the time of surgery.

As of May 1, 2001, more than 150,000 incontinence repair procedures using GYNECARE TVT Tension-Free Support for Incontinence have been performed worldwide. More than 40,000 have been performed in the U.S. The device is proven safe and effective when used
according to the Instructions for Use.

GYNECARE diligently reports to the Food and Drug Administration (FDA) all serious injuries and deaths in accordance with federal regulations. As of May 1, 2001, GYNECARE had reported 69 Medical Device Reports (MDRs) to the FDA involving complications of surgery. These reports include injuries to blood vessels of the pelvic sidewall and abdominal wall, hematomas, bladder and bowel injury and erosions.

The remaining MDRs included complications of a less serious nature such as hematoma, urinary retention and bladder perforation.

Most complications associated with the GYNECARE TVT Tension-free Support device are avoidable with scrupulous adherence to procedural technique and the instructions for use, rigorous attention to anatomy, careful patient selection, and vigilant attention to post-operative symptoms.

GYNECARE TVT Tension-free Support for Incontinence

What if...

Patient begins to move?

- Stop procedure
- Instruct anesthesiologist to increase sedation
- Evaluate anesthesia
- It is prudent to discuss the steps of the procedure with the anesthesiologist/anesthetist prior to procedure

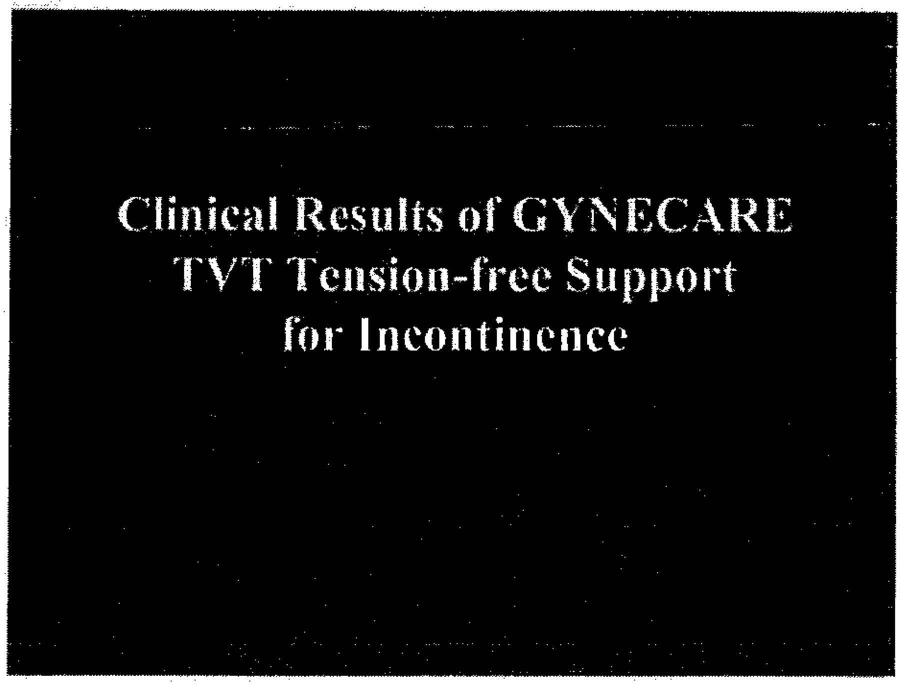
GYNECARE TVT Tension-free Support for Incontinence

What if...

You encounter resistance on passing the GYNECARE TVT needle?

- Check orientation and alignment
- Re-direct tip of needle by carefully maneuvering introducer handle
- Avoid using excessive force

GYNECARE TVT Tension-free Support for Incontinence


Clinical Results of GYNECARE
TVT Tension-free Support
for Incontinence

GYNECARE TVT Tension-free Support for Incontinence

Clinical Results:
GYNECARE TVT Tension-free Support for Incontinence

- Study of 75 patients reported in *Int'l Urogynecology Journal* (1996)
- 84% dry, 8% improved
- 2 year follow-up
- Mean OR time = 22 minutes
- No rejection or infections

GYNECARE TVT Tension-free Support for Incontinence

Clinical Results:
GYNECARE TVT Tension-free Support for Incontinence

- 1998 multicenter trial using same technique
- 131 patients (6 centers)
- SUI, no prolapse
- No infections or rejections
- 1 year follow-up: 91% dry, 7% improved

GYNECARE TVT Tension-free Support for Incontinence

Clinical Results: GYNECARE TVT Tension-free Support for Incontinence

- 3 year follow-up study
- *British Journal of Obstetrics and Gynecology*
- 50 patients
- GUSI, no urge or prolapse
- No rejection or erosion
- Pre and post-op urodynamics
- 86% dry, 12% significantly improved

GYNECARE TVT Tension-free Support for Incontinence

Pubo Vaginal Sling - PROLENE Tape
Subjective Results

Author (# pts)	Dry	Improvement	Success/Failure (%)
Ulmsten (75)[1]	63 (84%)	6 (8%)	69 (92%) / 6 (8%)
Ulmsten (131)[2]	119 (91%)	9 (7%)	128 (98%) / 3 (2%)
Wang (70)[3]	61 (87%)	3 (4%)	64 (91%) / 6 (9%)
Haab (62)[4]	54 (87%)	6 (10%)	60 (97%)/ 2 (3%)
Ulmsten (50)[1]	43 (86%)	6 (12%)	49 (98%)/ 1 (2%)
Total (388)	340 (88%)	30 (7%)	370 (95%) / 18 (5%)

1 - 2 year follow-up
2 - follow-up ≥ 12 months
3 - 3-18 months follow up
4 - 3 Year follow up

A large number of patients has undergone the procedure since 1995, verifying that the procedure is safe. Follow-up at 2 years indicates 84% cure. The procedure is safe and effective.

All recent peer reviewed clinical studies are included in the Preceptee binders.

GYNECARE TVT Tension-free Support for Incontinence

Pubo Vaginal Sling - PROLENE Tape
Intraoperative Results

Author	Mean OR Time	Bladder Perforation	Blood Loss > 300cc
Ulmsten	22 minutes	0	0
Ulmsten	26 minutes	1	0
Wang	29 minutes	3	0
Ulmsten	29 minutes	0	0

GYNECARE TVT Tension-free Support for Incontinence

Pubo Vaginal Sling - PROLENE Tape
Postoperative Complications

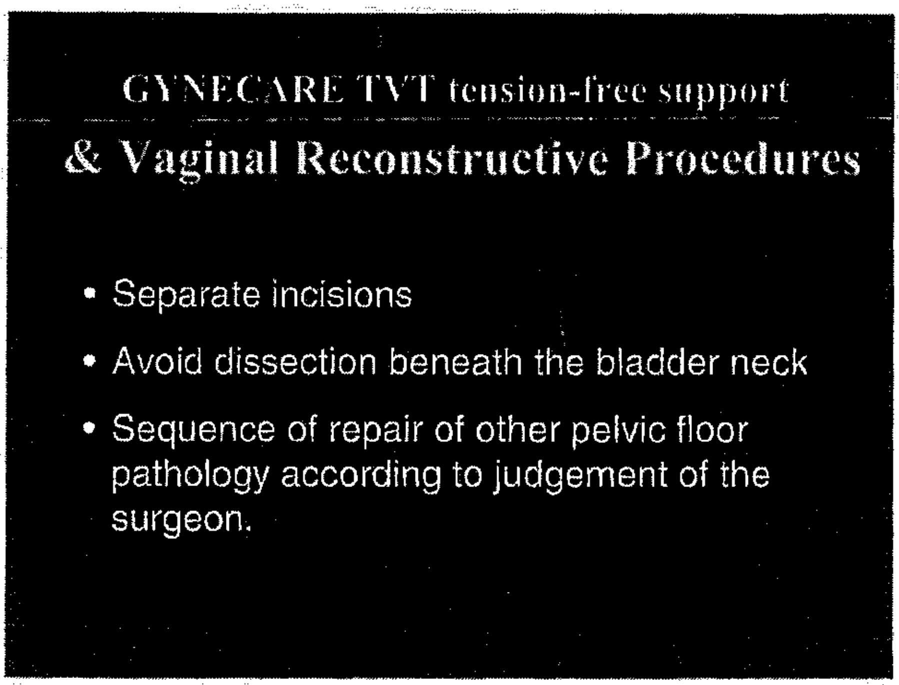
Author	Voiding Difficulty	UTI	Urge Incontinence	Miscellaneous
Ulmsten	5 (6%)	5 (6%)	0	0
Ulmsten	4 (3%)	N.R.	N.R.	2: 1 Wound Infection, 1 Hematoma
Wang	12 (17%)	4 (6%)	2 (3%)	N.R.
Ulmsten	10%	0	0	0

GYNECARE TVT Tension-free Support for Incontinence

Pubo Vaginal Sling - PROLENE Tape
Outcome of Surgery

Author	Hospital Stay	Mean time to return to work
Ulmsten	Same day or day after	10 days
Ulmsten	Same day or day after	14 days
Wang	Mean-3 days (2-8 days)	N.R.
Ulmsten	Same day or day after	N.R.

GYNECARE TVT Tension-free Support for Incontinence


GYNECARE TVT tension-free support
& Vaginal Reconstructive Procedures
• Separate incisions
• Avoid dissection beneath the bladder neck
• Sequence of repair of other pelvic floor pathology according to judgement of the surgeon.

EXHIBT A-4

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Original Article

A Multicenter Study of Tension-Free Vaginal Tape (TVT) for Surgical Treatment of Stress Urinary Incontinence

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Abstract: The aim of the study was to evaluate the safety and efficacy of TVT (tension-free vaginal tape) for the surgical treatment of stress urinary incontinence. The design was a prospective open multicenter study including six centers, each operating an approximately 20 patients. In total 131 patients suffering from genuine stress incontinence were included. They were followed for at least 1 year using a specific protocol for objective and subjective evaluation of the outcome. All patients underwent the operation under local anesthesia. Mean operation time was 28 minutes (range 19–41 minutes); 119 (91%) of the patients were cured according to the protocol and another 9 (7%) were significantly improved. There were 3 (2%) failures. The majority of the patients (about 90%) were operated upon on a day-care basis, which implied that they were released from the hospital within 24 hours, with no postoperative catheterization. No defect healing and no tape rejection occurred. Three patients needed an indwelling catheter for 3 days. In 1 patient catheterization was necessary for more than 10 days. Two uncomplicated hematomas and one uncomplicated bladder perforation occurred. Based on the results, we conclude that TVT is a safe and effective ambulatory procedure for surgical treatment of genuine stress urinary incontinence.

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Keywords: Local anesthesia; Stress incontinence; Surgery

Introduction

Recently we reported on an ambulatory surgical procedure for the treatment of female stress urinary incontinence [1]. The procedure, now called TVT (tension-free vaginal tape), is based on a series of experimental investigations of the urethral closure mechanism in females [2–6]. The results from the first reported study were promising, showing among 75 unselected stress incontinent females a complete cure rate of approximately 85% and another 7% considerably improved. All operations were, however, carried out in the Department of Obstetrics and Gynaecology, Uppsala University Hospital, by experienced urogynecologists who had been involved in the development of the procedure. This might have influenced the outcomes of the operations in as much as the results were 'too positive'. In particular, this statement might be considered when it comes to the few observed intra- and postoperative complications, considering that we are dealing with a sling-like procedure [7]. In order to find out how easy, effective and, above all, safe the procedure could be in 'ordinary' gynecologic units, it was decided to carry out a prospective multicenter study in Scandinavia. Apart from Uppsala, five other departments participated (Danderyd, Falun, Helsinki, NÄL and Wäxjö). The main aims were, as indicated above, to find out how safe and effective the procedure was, in particular the risks of intra- and postoperative complications, as well as the overall results and the surgeons' opinion of the procedure compared to previously used techniques.

Materials and Methods

According to the protocol each department should operate on about 20 patients a year. All should have genuine stress incontinence based on the medical history, the objective findings at gynecologic examination, including stress provocation test, pad test and urodynamic investigations [8]. The study was designed as a prospective open study according to the following.

Each center provided 2–3 patients for learning the procedure. A teacher from Uppsala visited each center and, together with one or two local surgeons, the TVT procedure was carried out according to the previously described technique [1]. The local team then carried out approximately 20 consecutive operations. The pre- and postoperative protocol included, as indicated above, a medical history, a gynecologic examination, including stress test (cough provocation test) with filled (~ 250 ml) bladder, a modified quality of life assessment including a visual analog scale (VAS) [9], 24-hour pad test and, when possible, a full urodynamic investigation [8]. In smaller units only single-channel cystometry was carried out. Postoperatively patients were assessed in the departments after 2, 6 and 12 months.

Patients

In total 131 patients were operated on. The women suffered from genuine stress incontinence, mean grade II (according to the Ingelman-Sundberg scale [10]). The duration of the incontinence symptoms was on average 3 years. No patient had been operated upon before for stress incontinence. The patients were unselected in as much as they were operated upon irrespective of a high or low resting urethral pressure, or normal or hypermobile urethra. No patient had signs or symptoms of prolapse. Mean age was 53 years (range 35–88), parity 2 (range 0–5). Postmenopausal patients were taking systemic or local estrogen therapy.

Surgical Procedure

TVT was carried out according to the previously described procedure [1]. The patient was operated on under local anesthesia using 0.25% prilocaine adrenaline as anesthetic. Two minimal incisions 5 cm apart were made in the abdominal skin just above the superior rim of the pubic bone. Then a 1.5 cm long sagittal incision was made in the vaginal wall, starting 1 cm from the external urethral meatus. After minimal bilateral paraurethral dissections of the vaginal wall a specific prolene tape (Ethicon) covered by a plastic sheath was introduced, using a previously described two-component needle instrument (Ethicon) [1]. The tip of this first perforated the urogenital diaphragm, and within the space of Retzius the needle tip (in close contact with the back of the pubic bone) was brought up to the abdominal incision. The procedure was then repeated on the contralateral side, placing the tape in a U shape around *midurethra.* After cystoscopy to ensure an intact bladder, the tape was adjusted *without tension* under the urethra. During this adjustment the patient was asked to cough to check that she had become continent by the procedure. Hereafter, the plastic sheath covering the Prolene tape was removed and, because of the strong friction between the tape and the tissue canals created, no fixation was carried out. The vaginal and abdominal incisions were closed after cutting the abdominal ends of the tape subcutaneously *without fixation.* One advantage of this procedure is that the surgeon can make sure that continence (i.e. no urinary leakage on cough provocation) has been obtained intraoperatively without any elevation of the urethra, thereby avoiding postoperative urinary retention. By the same token the operation is 'individualized', as the adjustment of the tape is carried out in consideration of each patient's individual tissue requirements. To achieve this the procedure must be performed under local anesthesia. After surgery the patient left the theater without postoperative catheterization. She was encouraged to move freely and micturate at the first desire to void.

Results

All patients were followed for ⩾12 months and all were operated on under local anesthesia. Mean operating time, including time for anesthesics to take, was 28 minutes (range 19–41).

Out of 131 patients 119 (91%) were cured, which means that they did not leak urine postoperatively, either objectively or subjectively. Positive results as assessed by the patient required a ⩾90% improvement in her life quality evaluation on the VAS to be accepted. Objective cure involved leakage <10 g/24 hour on pad testing as well as negative stress test on repeated coughs with a comfortably (250 ml) filled bladder.

Another 9 patients (7%) were found to be significantly improved, i.e. no leakage at stress test and a significantly decreased amount of leakage on the 24-hour pad test, as well as >75% improvement on VAS, with an occasional leakage only on severe cold etc.

In 3 patients an improvement was noted but it did not meet the criteria of significant improvement as presented above, and the patients were therefore classified as failures.

There were few intra- and postoperative complications. Thus only 1 bladder perforation occurred and 1 wound infection in the vaginal wall incision. This did not affect the outcome of the procedure in either case, and both patients became continent. In the patient with bladder perforation the tape was reinserted intraoperatively. After using an indwelling catheter for 2 days she voided without residual urine. The patients with wound infection had vaginal wall atrophy. After a minimal vaginal wall resection and effective local estrogen treatment she healed without further intervention. There was no tape rejections.

In 3 patients short-term (⩽3 days) postoperative urinary retention occurred, requiring an indwelling catheter for 3 days. In 1 further patient with voiding problems for 12 days a small adjustment of the tape was made via the vaginal incision, after which micturition was normalized.

In 1 patient a retropubic hematoma initially the size of a hen's egg was observed. It was followed by ultrasound and vanished without further intervention.

All patients, apart from those specifically mentioned above, were released from hospital the day after the operation. Sick leave was approximately 2 weeks (range 10–21 days).

Discussion

The results from this multicenter study are about the same as those reported previously [1,11–16], i.e. the operation times were short and complications few. In the majority of centers surgeons without specific training in urogynecologic surgery were involved, and their results were as good as those in the more experienced centers. In fact, the only bladder perforation occurred in Uppsala, where the technique had been developed. In all centers the method has now, after due consideration by the involved surgeons, been adopted as the primary technique for the surgical treatment of stress urinary incontinence. Ongoing follow-up studies indicate no significant deterioration of the results over time (observations to be published). This finding is in accordance with a recently completed follow-up study of 45 patients in one of the departments (Uppsala) that showed no significant deterioration in the results (90% cure rate) over a 3-year period [17].

Most encouraging is the low complication rate in 'less experienced' hands, which might be due to the fairly simple and well standardized technique and the use of the specific instruments which, when properly handled, will carry out the work. By the same token the few postoperative urine retention problems can be ascribed to the specific technique using a tension-free vaginal tape, as emphasized above. In this context it is important once again to emphasize that the tape is only loosely placed under the midurethra, and that no elevation is allowed. Postoperative urinary retention is thus avoided without effects on the obtained continence. It should also be emphasized that TVT must not be compared to a traditional bladder neck elevation sling procedure.

Another important finding worth emphasizing is that no tape rejection occurred. Again this may be due to the specific tape material (Prolene, Ethicon, covered by a plastic sheath). This positive observation is in contrast to that found in previous investigations using a similar surgical technique but with other tape materials, such as Teflon, Gore-Tex, Mersilene and Marlex. Under these circumstances rejection rates of approximately 10% occured [2,3,17].

Conclusion

From the present result it seems justified to conclude that TVT can be considered a safe and effective procedure for the surgical treatment of genuine female stress incontinence. It can be carried out in a standardized way under local anesthesia on a day-care basis. The cure rate seems to be as good as that reported with traditional surgical procedures, although long-term follow-up studies have to be presented before any definitive conclusions can be made. Preliminary results from such studies, however, indicate that the short-term results presented here do not change significantly over time.

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EDITORIAL COMMENT: This is the first prospective study of a relatively new and minimally invasive surgical procedure for stress urinary incontinence. The authors are to be complimented on the fact that they went out into the community hospitals in their area to see if their results could be reproduced by the average practicing gynecologist. Also, it is good to see that the investigators used a validated quality of life assessment to provide very important follow-up information on the improvement in the patient's quality of life, as this should be the basic tenet of all therapies for urinary incontinence. However, many questions remain regarding the diagnostic criteria they used in selecting their patients, as well as the degree of testing performed postoperatively. Further study is needed to confirm the results found here with a very new and interesting technique in the surgical treatment of stress incontinence.

EXHIBT A-5

SCANDINAVIAN MULTICENTER STUDY OF THE TENSION FREE VAGINAL TAPE PROCEDURE

CLINICAL REPORT

M. Eriksson (MEDSCAND)
October 17, 1997

1. INTRODUCTION AND BACKGROUND

Stress urinary incontinence (SUI) is a very common affliction in women. Recent research indicates that the pathophysiology of SUI involves defects in the supporting tissues that help stabilize the urethra in its correct anatomical position. The tissues involved are the anterior vaginal wall which supports the urethra and bladder neck, the pelvic floor muscles which are in part connected to the urethra and vaginal wall and, primarily, the pubo-urethral ligaments that attach the urethra and vaginal wall to the symphysis pubis and the pubic bone. The connective tissue interconnecting the structures mentioned above is also of prime importance. If there is a defect in any of these structures, there will be insufficient closure forces acting on the urethra at moments of physical stress with urine being passed through the urethra as a result. Although the condition of the urethra itself is not without importance, it seems likely that the state of the supporting structures is what finally decides whether or not continence can be maintained.

For many decades, various surgical procedures have been used to try to alleviate SUI. These have been either vaginal where the objective has been to tighten the supporting structures beneath the urethra, or supra-pubic procedures where the urethra has been apposed to the posterior surface of the pubic bone. Different sling procedures have also been in common use. In these procedures, a sling, made either of autologous, homologous (cadaveric) or synthetic material, has been introduced in a U-shape beneath the urethra and attached to the anterior abdominal wall or ligamentous structures in connection to the pubic bone.

The tension free vaginal tape procedure (TVT) is a recently developed surgical procedure to treat SUI. It has been used at Akademiska sjukhuset, Uppsala and at collaborating Swedish and Scandinavian centers for some years. Using a specially designed introducer, a sling is placed para-urethrally by way of a small vaginal incision. The main advantage of this method is its simplicity. The operation can and should be carried out under local anesthesia. This allows the surgery to be offered to women who are not candidates for general anesthesia. As a result, the patient can cooperate fully during the operation. By letting the patient cough, the surgeon is able to achieve optimal tension of the sling, thereby securing continence while at the same time avoiding difficulties of voiding and long catherization periods post-operatively. The length of hospitalization as well as the time the patient has to spend on sick leave can thus be reduced. The resulting continence rate is comparable to that of the more extensive procedures.

2. OBJECTIVES

The aim of the present study was to determine the short-and long-term efficacy and safety of the tension free vaginal procedure using a Prolene™ mesh in women with stress incontinence. In addition, this study was designed to extend the results found in earlier work (1) into a multi-center setting.

The clinical trial was designed as an open, non-randomized, prospective, multi-center study. The primary end points were effectiveness of the procedure, operative and post-operative complications, as well as patient feedback.

3. MATERIALS AND METHODS

Six medical centers in Scandinavia enrolled the patients described in this report. The primary inclusion for entry into the study was a diagnosis of stress urinary incontinence. This diagnosis was based on 1) a medical history of urine leakage associated with exercise, 2) 48 hour micturition diary, 3) pad testing, and 4) stress testing. A quality of life assessment which included use of a visual analog scale was also performed. In addition, all patients entered gave informed consent.

Patients with significant vaginal prolapse, those with previous surgery for uterovaginal prolapse or stress incontinence and those with residual urine greater than 100 ml were excluded. In addition, patients with ongoing urinary tract infections were also not entered.

TVT was carried out according to a previously described procedure (1). Briefly the patient was operated under local anaesthesia using 0.25% Prilocain adrenaline as an anaesthetic. Two minimal incisions, 5 cm apart were made in the abdominal skin just above the superior rim of the pubic bone. A 1.5 cm long sagittal incision was made in the anterior vaginal wall starting 1 cm from the external urethral meatus. After minimal dissection of the urethra from the vaginal wall, a specific Prolene™ tape covered by a plastic sheath was introduced using an introducer previously described (1). The needle instrument first perforated the urogenital diaphragm and within the cavum Retzii the needle, in close contact with the back of the pubic bone, was brought up to the abdominal incision. The procedure was then repeated on the contra lateral side. Thereby the tape was placed in a U-formed shape around the mid-urethra. After cystoscopy assured an intact bladder, the tape was adjusted without tension under the urethra. During this adjustment the patient was asked to cough making sure that she had become continent by the procedure. Hereafter the plastic sheath of the tape was removed and due to the strong friction between the specific Prolene™ tape and the tissue no further fixation was done. The vaginal and abdominal incisions were closed after cutting the abdominal ends of the tape in the subcutis without any fixation.

Patients were monitored during the procedure and at the post-operative recovery period. Duration of the surgical procedure as well as perioperative complications were recorded. In addition, postoperative complications were also monitored; these included voiding dysfunction,infection and hematoma.

The patients were then followed up at 2 months, 6 months and 12 months after surgery. Followup included subjective evaluation of incontinence, 48 hour micturition diary, residual urine determination and stress testing.

PRELIMINARY RESULTS

At the time of analysis (May, 1997), 131 patients had entered into the study at six centers. The mean age of the women was 53.08 years with a range of 35 to 86 years; median parity was 2. The majority of the postmenopausal women were on either local or systemic estrogen therapy.

The preliminary efficacy results are summarized in Table I. Of the 131 patients, nine had only been evaluated at two months, 32 through the six month evaluation while the remaining 90 had completed the 12 month visit. Of these, two had minimal benefit from the procedure, five were considerably improved while the remaining 124 patients were considered cured based on the above subjective and objective criteria.

Table II tracks the same group of patients for operative and postoperative complications. Seven complications were noted including four cases of urinary retention (delayed voiding), one case of bladder perforation, one case of hematoma and one case of vaginal wound infection. Three of the four cases of retention were resolved with catherization for one to three days; the fourth required intervention. The hematoma resolved over time without treatment while the vaginal infection required surgical intervention with resection of exposed mesh. No cases of rejection of the Prolene graft were noted.

Conclusions and Discussion

It was interesting to note that the five centers performed at least as well as the Uppsala center where the technique was developed. This is noted both in the tabulation of the efficacy results as well as the number of complications noted. Overall the efficacy noted was very similar to the original study and seems to indicate that this procedure may be transferred from one center to another with minimal loss in success rates.

Also noteworthy was the fact that no cases of graft rejection was seen in this series. Normally one would expect on the order of a three percent rejection rate with traditional slings (as evidenced by vaginal/urethral erosion). (2) Also noteworthy is the lack of retention problems. A recent review of the literature indicates that retention longer than four weeks is seen in 8% of sling cases (2). In this series only four patients had voiding problems which resolved during a one to three day period.

In summary these preliminary results corroborate earlier studies which concluded that this procedure could provide the traditional high cure rates seen with sling surgery, but had the additional advantages of being able to be performed under local anesthesia, short hospitalization stay and minimal postoperative morbidity. As with any surgery for stress urinary incontinence, longer followups will be necessary to assess the long term potential of this procedure in maintaining continence.

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Margareta Eriksson, M.D., Ph.D.
Medscand Medical

Oct 17, 1997
Date

ETH.MESH.08476340

TABLE 1

PRELIMINARY RESULTS
EFFICACY

Centre	Number Included Patients	2 Months Visit	6 Months Visit	12 Months Visit
Falun	21	H:2	H:8	H:10/B:1
Växjö	30	H:3	H:7	H:20
NÄL	20		H:5	H:15
Danderyd	19			H:15/B:3/O:1
Uppsala	22	H:4	H:4	H:12/B:1/O:1
Helsinkl	19		H:8	H:11
	131	H:9	H:32	H:83/B:5/O:2

H = Cured
B = Considerable Improved
O = Unchanged

TABLE 2

PRELIMINARY RESULTS

Operative and Postoperative Complications

	Falun	Dand	Helsinki	NÄL	Växjö	Uppsala
n=131	21	19	19	20	30	22
perioperative bleeding >300 ml	0	0	0	0	0	0
bladder perforation	0	0	0	0	0	1
vaginal wound infect.-surgical intervent.	0	0	0	1	0	0
retention (catheterization)	0	0	0	0	0	3
retention (intervention)	0	1	0	0	0	0
Hematoma	1	0	0	0	0	0